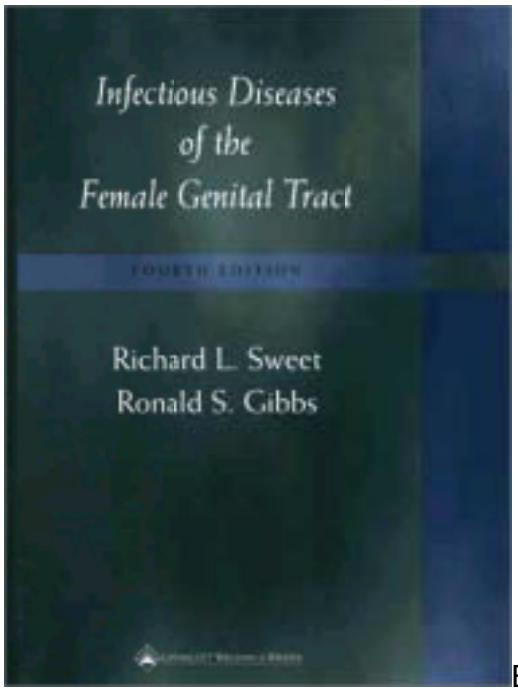
Infectious Diseases of the Female Genital Tract, 4th edition: by Richard L., Md. Sweet, Ronald S., MD Gibbs By Lippincott Williams & Wilkins Publishers (January 15, 2002)



By OkDoKeY

Infectious Diseases of the Female Genital Tract

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ANTIBIOTICS/ANTIVIRALS

IMMUNIZATION

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ACKNOWLEDGMENT

We acknowledge the administrative and editorial assistance of Phyllis Catrell, Jane Cook, and Susan Kostilnik in the preparation of this edition.

DEDICATION

This book is dedicated to our wives, Rhea and Jane, for their continued love, support and understanding. To our children, Jennifer, Suzanne, Andrew, Eric, and Stuart and our grandchildren Hanna, Dylan, Benjamin and Emily and future grandchildren who provide us with the ongoing spark and impetus for our continued commitment to this work.

PREFACE

During the writing of this fourth edition of *Infectious Diseases of the Female Genital Tract*, infections seem to have played an ever-expanding role, not only in the practice of obstetrics and gynecology but in the practice of medicine in general. Regularly the news media produced stories about new infections and antibiotic resistance. These, indeed, continue to be challenging and exciting times in the world of infectious diseases.

For this fourth edition, we have maintained the goal of providing physicians with up-to-date knowledge that—in a highly readable form—deals with infectious diseases in the female. We have substantially revised and updated every chapter and have added several eye-appealing features. We are especially pleased that accompanying this fourth edition will be an atlas to add to the usefulness of this text.

We have been gratified by the place this text has earned in the offices and libraries of many obstetricians and gynecologists, and we thank the readers for their support.

1

CLINICAL MICROBIOLOGY OF THE FEMALE GENITAL TRACT

The microbiology of the female genital tract is indeed complex. In healthy women, the vagina contains 10^9 bacterial colony-forming units per gram of secretions. Isolates commonly found in the lower genital tract include a variety of aerobic and anaerobic bacteria, yeast, viruses, and parasites (Table 1.1). Influences upon these microbes include phase of the menstrual cycle, sexual activity, contraceptive use, childbirth, surgery, and antibiotic therapy. The upper genital tract usually is sterile, but bacteria from the lower genital tract may ascend into the uterine cavity, fallopian tubes, or pelvic peritoneum because of menstruation, instrumentation, foreign bodies, surgery, or other predisposing factors.

Bacteria (aerobes, facultative, and anaerobes)
Intracellular bacteria (*Chlamydia trachomatis*)
Mycoplasmas
Viruses
Yeasts
Parasites

TABLE 1.1. OVERALL CLASSIFICATION OF MICROORGANISMS FOUND IN THE FEMALE GENITAL TRACT

This chapter presents a working knowledge of genital tract microbes for the clinician. More detailed descriptions of selected microbes are provided in other chapters.

VIRULENCE

Distinguishing “virulent” or “pathogenic” isolates from “nonvirulent” or “nonpathogenic” ones often is difficult because the behavior of a given isolate is so dependent upon the numbers of isolates present, host factors, and local conditions (presence of necrosis and foreign body). For example, although group B streptococcus is a leading cause of maternal and neonatal septicemia, most women with genital colonization by group B streptococci (GBS) suffer no consequences. On the other hand, *Staphylococcus epidermidis* is generally considered a low-virulence organism and is commonly considered part of the normal skin and vaginal flora, but it also may cause disease when conditions allow. For example, *S. epidermidis* has been recognized as a cause of infective endocarditis of neurologic shunts.

Despite such widely ranging behavior patterns, it still is practical to distinguish “high”- from “low”-virulence genital isolates. For practicality, the bacteria are divided into aerobes and anaerobes. Each of these groups is subdivided further into Gram-positive and Gram-negative organisms.

AEROBIC ORGANISMS

Gram-Positive Cocci

The organisms in this group include the aerobic streptococci and staphylococci (Table 1.2).

TABLE 1.2. ANTIBIOTIC THERAPY FOR AEROBIC AND FACULTATIVE BACTERIA FOUND IN FEMALE GENITAL INFECTIONS

Streptococci

Many varieties of streptococci have been found in the pelvis, and they have been classified by two independent schemes. In one scheme, the streptococci are distinguished by their hemolytic properties on blood agar plates. Aerobic streptococci showing partial (or green) hemolysis are termed alpha (a) streptococci, those showing complete (or clear) hemolysis are termed beta (b) streptococci, and those showing no hemolysis are termed gamma (g) streptococci. In the other scheme, the Lancefield system, many streptococci can be classified according to surface antigens, designated by the letters A through O. In humans, streptococci of groups A, B, and D are common pathogens. Group A and B streptococci nearly always produce b hemolysis. Group D streptococci usually are nonhemolytic (g streptococci), but on occasion they may be either a or b hemolytic as well.

Group A Streptococci *(Streptococcus pyogenes)*

Streptococcus pyogenes causes pharyngeal, cutaneous, puerperal, and postoperative infections and necrotizing fasciitis. Sequelae of group A streptococcal infections may include rheumatic fever and acute glomerulonephritis. It is not generally considered to be a member of the normal vaginal flora, as it is isolated in less than 1% of asymptomatic women. Pelvic infection caused by group A streptococci may produce a characteristic clinical picture, with a high, early initial fever, chills, prostration, and diffuse tenderness. Historically, the group A b-hemolytic streptococcus was the organism responsible for fatal puerperal sepsis. On Gram stains, one sees Gram-positive cocci in chains. The microorganism remains exquisitely sensitive to penicillin, and erythromycin or a cephalosporin usually can be substituted for treatment of the penicillin-allergic patient. Clindamycin is an alternative agent, as is vancomycin.

Group A streptococcal pelvic infections occur in both sporadic and epidemic forms. Epidemics usually are exogenous in origin, commonly resulting from nasopharyngeal carriage of the microorganism or from skin infections in hospital staff members.

Occasionally, a mother may be the source.

Epidemics can be prevented by placing patients with group A streptococcal infections in strict isolation and by early antibiotic treatment of hospital employees with group A streptococcal infections. Employees with positive cultures should be relieved of duty on obstetric, neonatal, and postoperative wards until their cultures become negative. When epidemics have occurred, isolation and antibiotic therapy have not always sufficed to effect control. In some recent outbreaks, additional measures, such as identifying and treating all streptococcal carriers, canceling elective surgery, and prophylactic treatment of all patients and personnel, have been necessary.

Group B Streptococci *(Streptococcus agalactiae)*

Before the 1960s, GBS were not recognized as frequent pathogens, but they have now become a major cause of sepsis among neonates and postpartum women (see Chapter 3) (1,2). Unlike group A streptococci, group B organisms are considered part of the normal vaginal flora and can be recovered in about 20% of normal pregnant women. Isolation rates are enhanced by use of selective broth containing nalidixic acid and gentamicin. The clinical picture of GBS infection in puerperal women closely resembles that of group A infection. Epidemic GBS disease has not been reported among mothers, however. The neonate with GBS sepsis usually acquired the microorganism from the maternal genital tract. Even with appropriate therapy, early-onset neonatal GBS infection has a high fatality rate. In 1996, national guidelines were established to prevent GBS perinatal sepsis (see Chapter 3) (1,2).

Group B streptococci are susceptible to penicillin, ampicillin, and the cephalosporin group of antibiotics. Although erythromycin and clindamycin are considered alternatives to penicillin, recent reports have documented a rising resistance rate among GBS (3).

Group D Streptococci

This group is composed of two subgroups: “group D enterococci” and “group D not enterococci.” The former, which includes *Streptococcus faecalis, Streptococcus faecium,* and other less common species, occurs frequently. Although these organisms cause endocarditis and urinary tract infection, their virulence in genital infections has been debatable. They are considerably less virulent than group A or B streptococci, but on occasion they have caused serious genital and abdominal infections. Enterococci are important pathogens, particularly in situations where cephalosporin prophylaxis has been used (4). They are the only streptococci not sensitive to penicillin. They are resistant to cephalosporins, alone or in combination with aminoglycosides (streptomycin, kanamycin, or gentamicin), and to clindamycin, alone or in combination with aminoglycosides. Enterococci organisms are susceptible to ampicillin, to penicillin or ampicillin and aminoglycoside in combination, and to vancomycin. Of recent concern have been reports of enterococcal resistance to ampicillin-aminoglycoside combination and vancomycin, but these appear rarely in pelvic infections (5). Failure of a patient to respond to cephalosporin-aminoglycoside or clindamycin-aminoglycoside combinations may be seen when the primary pathogen is an enterococcus (4).

Nonenterococcal group D streptococci can be commonly isolated. They are susceptible to penicillin.

Other Aerobic Streptococci

Other aerobic streptococci include a variety of common bacteria that are susceptible to penicillin. Examples are a and g streptococci. The most important of these are the viridans group streptococci, which include *Streptococcus intermedius* (*Streptococcus milleri* group), *Streptococcus mitis, Streptococcus mutans, Streptococcus oralis, Streptococcus parasanguis, Streptococcus salivarius,* and *Streptococcus sanguis.*

Streptococcus pneumoniae is an uncommon but potentially serious cause of genital tract infections.

Staphylococci

The aerobic staphylococci include *S. epidermidis, Staphylococcus saprophyticus (Micrococcus),* and *Staphylococcus aureus.* The first two do not produce a coagulase enzyme (the “coag-negative” staphylococci), whereas *S. aureus* does (“coag-positive” staphylococci). *Staphylococcus aureus* is isolated from 5% to 10% of genital tract cultures. This organism has been recognized as a cause of abdominal wound infections, breast abscesses, and nursery outbreaks of infection. It has been isolated from nearly all patients with toxic shock syndrome. Most species of *S. aureus,* whether isolated in the community or in the hospital, elaborate penicillinase and are resistant to penicillin and ampicillin. Agents of choice for treatment of *S. aureus* infections are the penicillinase-resistant penicillins, such as cloxacillin, dicloxacillin, methicillin, oxacillin, and nafcillin. Resistance to these antibiotics by methicillin-resistant *S. aureus* has become a major nosocomial infection problem (6). Antibiotics for use in *S. aureus* infections in the penicillin-allergic patient are the “first-generation” cephalosporins and clindamycin. Vancomycin is the drug of choice for methicillin-resistant *S. aureus.*

Staphylococcus saprophyticus has been recognized recently as an important cause of urinary tract infection. This organism is susceptible to a wide range of antibiotics, including penicillins, cephalosporins, and trimethoprim-sulfamethoxazole (TMP-SMX). *Staphylococcus epidermidis* is commonly isolated from the vagina and skin, but rarely causes infection. Conditions in which *S. epidermidis* is recognized as a pathogen include osteomyelitis, possibly late-onset neonatal sepsis, and association with foreign bodies and invasive lines.

Gram-Positive Bacilli

The Gram-positive bacilli are common organisms in the normal vaginal flora (Table 1.2). *Lactobacillus* sp are the most frequent component of the normal vaginal flora in women of reproductive age. Although lactobacilli are generally nonvirulent organisms, the strains that produce hydrogen peroxide play a major role in controlling the vaginal flora. In unusual circumstances, the usually avirulent lactobacilli may produce invasive disease, such as bacteremia, which occurs in patients with underlying conditions such as cancer, recent surgery, and diabetes mellitus. Many of these patients received prior antibiotic therapy (7). When

lactobacilli appear in cultures of the urine, it almost certainly represents a contamination.

Listeria monocytogenes is present rarely in the vaginas of healthy women. Although the predominant route for severe intrauterine infections due to this organism during pregnancy is transplacental secondary to bacteremia, on occasion *L. monocytogenes* ascends from the lower genital tract to cause intrauterine infection (see Chapter 16). Epidemics due to *Listeria* organisms have occurred from contaminated dairy products.

Gram-Negative Bacilli

The Gram-negative bacilli include a large number of microorganisms with highly variable patterns of antimicrobial susceptibility. Many species have been identified, but only a few are commonly isolated from patients with pelvic infections (Table 1.2).

Escherichia Coli

Escherichia coli is one of the most common members of this group isolated in genital tract and urine specimens. It is present in approximately 70% of urinary tract infections. *Escherichia coli* infections usually are mild, but occasionally they may be fulminant, as it is the microorganism most commonly identified in bacteremic obstetric and gynecologic patients. *Escherichia coli* frequently is recovered in mixed infections of the pelvis, such as amnionitis, endometritis, and posthysterectomy cellulitis. Its susceptibility to antibiotics varies from hospital to hospital and, probably, from service to service. Gentamicin, tobramycin, amikacin, and chloramphenicol usually are effective against more than 95% of *E. coli* isolates. Increasingly, *E. coli* resistance to ampicillin has emerged. In general, more than 40% of *E. coli* (including community-acquired strains) are resistant to ampicillin. The first-generation cephalosporin antibiotics have remained active against *E. coli* isolates in most hospitals, but the newer cephalosporin agents (second and third generation) and newer penicillins are more active. The new quinolone agents, such as ciprofloxacin and ofloxacin, are very active against *E. coli,* as is TMP-SMX.

Gardnerella vaginalis

Formerly known as *Haemophilus vaginalis* and *Corynebacterium vaginale, Gardnerella vaginalis* is found in vaginal cultures of nearly all women with bacterial vaginosis, but it also can be found in vaginal cultures of 40% to 60% of asymptomatic women when a selective medium is used. It has been reported to cause endometritis and bacteremia. In some institutions, *G. vaginalis* is the most common Gram-negative aerobe recovered from the endometrium and blood of patients with postpartum endometritis. *Gardnerella vaginalis* has been frequently recovered from patients with pelvic inflammatory disease. Rather than being a pathogen on its own, *G. vaginalis* probably is involved by association with other bacterial vaginosis organisms. *In vitro* testing shows this organism to be susceptible to ampicillin and tetracycline, but these agents are of limited value in curing bacterial vaginosis (see Chapter 12).

Klebsiella *Species*

Klebsiella sp are found in less than 10% of genital tract infections, but they also cause urinary tract infections and hospital-acquired pneumonia. *Klebsiella pneumoniae* is the most common member of this group recovered from genital tract and urinary tract infections. *Klebsiella oxytocia* is much less common. All the cephalosporin antibiotics are highly effective against *Klebsiella* organisms, as are the aminoglycosides and chloramphenicol. Ampicillin has little activity, but some of the newer penicillins, such as piperacillin and mezlocillin, have improved activity. Quinoline agents are effective, as are the new enzyme-blocking drugs, such as amoxicillin (Augmentin), ticarcillin (Timentin), ampicillin (Unasyn), and piperacillin (Zosyn).

Enterobacter *Species*

Although closely related to *Klebsiella* species, *Enterobacter* species are encountered much less frequently (less than 5% of genital infections). They are more resistant to antibiotics than are *Klebsiella* species. Until recently, *Enterobacter* infections usually required therapy with aminoglycoside antibiotics, but some of the newer cephalosporins and newer penicillins show good activity. The most common of this group are *Enterobacter aerogenes* and *Enterobacter cloacae.*

Proteus *Species*

Proteus sp are isolated in 10% to 15% of genital tract infections and in a similar percentage of urinary tract infections. *Proteus mirabilis,* by far the most commonly isolated species in obstetric and gynecologic patients, is susceptible to ampicillin and the cephalosporins, as well as the aminoglycosides. *Proteus vulgaris* occurs much less commonly. Former *Proteus* species, *Proteus morganii* and *Proteus rettgeri,* are now classified as *Morganella morganii* and *Providencia rettgeri,* respectively. These species are resistant to ampicillin and the first-generation cephalosporins, but they are sensitive to the aminoglycosides and some of the newer penicillin and cephalosporin antibiotics.

Pseudomonas *Species*

Opportunistic pathogens in severe, usually hospital-acquired, infections, *Pseudomonas* sp are found infrequently in infections in obstetrics and gynecology, but *Pseudomonas* colonization is seen commonly in patients receiving antibiotic therapy. Antibiotic susceptibility is good to gentamicin and usually better to tobramycin and amikacin. Activity of the newer penicillins and some of the newer cephalosporins is good, and combinations of antibiotics may produce higher cure rates in serious infections.

Other Gram-Negative Bacilli

Other Gram-negative bacilli include microorganisms such as *Serratia, Citrobacter, Acinetobacter,* and *Providencia* species, all of which show resistance to commonly used antibiotics. Fortunately, these species are found rarely among obstetric and gynecologic patients, except in those who are debilitated or who are receiving antibiotic, immunosuppressive, or cytotoxic therapy.

Gram-Negative Cocci

In pelvic infections, the only significant member of the Gram-negative cocci is *Neisseria gonorrhoeae,* which may produce an asymptomatic colonization of the cervix, cervicitis, or salpingitis (Table 1.2). Disseminated infection with septicemia, arthritis, and dermatitis occurs not infrequently. *Neisseria gonorrhoeae* is a common cause of neonatal conjunctivitis and has been reported recently as an unusual cause of amnionitis and fetal scalp abscess. Penicillinase-producing strains of *N. gonorrhoeae* have become a major problem in the United States. In addition, chromosomally mediated resistance and tetracycline resistance have emerged in *N. gonorrhoeae.* Penicillin is no longer a recommended antibiotic. Cephalosporins or quinolones are preferred, usually in single-dose regimens, for uncomplicated gonococcal infections (8).

ANAEROBIC ISOLATES

Anaerobic bacteria are likely to produce infection in the presence of traumatized or devitalized tissue, and often they produce a feculent odor (9). Anaerobic bacteria are major pathogens in obstetric and gynecologic infections (Table 1.3).

Anaerobic Bacteria	Recommended Antibiotic(s)	Alternative Antibiotic(s)
Gram-positive cocci		
Peptostreptococcus	Penicillin, clindamycin, metronidazole	Cefoxitin, selected other cephalosporins
Peptostreptococcus anaerobius		
Peptostreptococcus asaccharolyticus		
Peptostreptococcus magnus		
Peptostreptococcus prevotii		
Gram-positive bacilli		
Actinomyces sp	Penicillins	Most cephalosporins, tetracycline, rifampin
Propionibacterium sp*	Rarely cause pelvic infection	
Clostridium perfringens	Penicillin, clindamycin, cefoxitin	Chloramphenicol, imipenem
Clostridium sp	Usually penicillin, metronidazole, clindamycin	
Clostridium difficile	Metronidazole, vancomycin	
Gram-negative bacilli		
Bacteroides (Bacteroides fragilis group)	Metronidazole, selected penicillin β-lactamase inhibitors, imipenem	Cefoxitin, cefotetan, clindamycin
Bacteroides sp, other	Clindamycin, metronidazole, cefoxitin, penicillin β-inhibitors, cefoxitan	Selected other cephalosporins
Fusobacterium sp		
Porphyromonas asaccharolytica		
Prevotella bivia		
Prevotella disiens		
Prevotella melaninogenica		

*Species generally with low virulence

TABLE 1.3. ANTIBIOTIC THERAPY FOR ANAEROBIC BACTERIA FOUND IN FEMALE GENITAL INFECTION

Gram-Positive Anaerobes

Peptostreptococcus *Species*

All species formerly classified as *Peptococcus,* except *Peptococcus niger,* have been transferred into the genus *Peptostreptococcus* (9). These strictly anaerobic cocci are isolated very commonly in the vagina and in cultures from obstetric and gynecologic infections. The most common of these organisms include *Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus, Peptostreptococcus prevotii, and Peptostreptococcus tetradius* (Gaffkya anaerobia).

Penicillin is the drug of choice for infections known to be caused by peptostreptococci, but clindamycin, metronidazole, cefoxitin, cefotetan, first- and third-generation cephalosporins, and chloramphenicol are highly effective for the penicillin-allergic patient or for broader anaerobic coverage.

Clostridium *Species*

Strictly anaerobic, plump, Gram-positive rods, clostridia may be isolated from vaginal secretions of 5% to 10% of asymptomatic women. Clostridia are anaerobic, spore-forming rods that can produce potent toxins and result in severe life-threatening infections. The most commonly isolated species is *Clostridium perfringens* (also known as *Clostridium welchii*). Other clinically important clostridia include *Clostridium novyi, Clostridium ramosum, Clostridium septicum,* and *Clostridium sordelli.* Although clostridial species may produce gas gangrene (with septicemia, circulatory collapse, hemolysis, and peritonitis), they are more commonly associated with a much less disseminated infection that responds promptly to appropriate antibiotic therapy. Simply isolating this microorganism from a pelvic site does not, therefore, indicate life-threatening infection or the need for a hysterectomy. Initial therapy for clostridial infections usually consists of intravenous administration of large doses of penicillin and close patient monitoring. If signs of extension of infection become apparent, debridement (often by transabdominal hysterectomy and bilateral salpingo-oophorectomy) is required. These signs include worsening clinical condition or failure to respond promptly; parametrial tenderness, crepitus, or myalgia; or hypotension, falling central pressure measurements, or oliguria despite adequate volume replacement. Radiographic findings of interstitial gas are uncommon and develop late in the clinical course, but an abdominal x-ray film should be obtained.

Clostridium difficile is isolated infrequently in genital tract infections but is pathogenic in antibiotic-associated pseudomembranous colitis. *Clostridium difficile* is resistant to many antibiotics, but it can be treated with metronidazole or vancomycin (Table 1.3).

Propionibacterium, Eubacterium, *And* Bifidobacterium *Species*

These Gram-positive anaerobic bacilli usually are isolated in anaerobic specimens. They are organisms of low virulence and most often do not require specific antibiotic therapy.

Gram-Negative Anaerobes

Bacteroides

In the early 1990s, the genus *Bacteroides* underwent major taxonomic revisions (9). This revision was necessitated by the large heterogeneity in biochemical and chemical properties demonstrated in this group of microorganisms. The genus *Bacteroides* now only includes species that were formerly described as the "*Bacteroides fragilis* group." *Bacteroides* now includes the species *B. fragilis, Bacteroides caccae, Bacteroides distasonis, Bacteroids eggerthii, Bacteroides merdae, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis,* and *Bacteroides vulgatus* (Table 1.3).

New genera have been established that include many of the microorganisms

previously classified as *Bacteroides.* Table 1.4 lists the changed designations of species associated with genital tract infections that were formerly classified as *Bacteroides.* The two major new genera are *Prevotella* and *Porphyromonas.* The most important of these microorganisms in the pathogenesis of obstetric and gynecologic infections are *Prevotella bivia* (formerly *Bacteroides bivius*), *Prevotella disiens* (formerly *Bacteroides disiens*), *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*), and *Porphyromonas asaccharolytica* (formerly *Bacteroides asaccharolyticus*). The taxonomic position of several non-*B. fragilis* group species of *Bacteroides* remains to be determined. These currently are listed as *Bacteroides* species other and include *Bacteroides capillosus, Bacteroides coagulans, Bacteroides splanchnicus,* and *Bacteroides ureolyticus* (Table 1.3).

Old Classification	New Classification
Bacteroides fragilis group	*Bacteroides*
Bacteroides bivius	*Prevotella bivia*
Bacteroides disiens	*Prevotella disiens*
Bacteroides corporis	*Prevotella corporis*
Bacteroides intermedius	*Prevotella intermedia*
Bacteroides melaninogenicus	*Prevotella melaninogenica*
Bacteroides asaccharolyticus	*Porphyromonas asaccharolytica*

TABLE 1.4. NEW NOMENCLATURE OF MICROORGANISMS ASSOCIATED WITH GENITAL TRACT INFECTIONS THAT WERE FORMERLY MEMBERS OF THE GENUS *BACTEROIDES*

These are strictly anaerobic bacilli that produce infections that often are protracted. From studies of obstetric infection, the most commonly identified species is *P. bivia,* which is isolated in 20% to 40% of obstetric and gynecologic infections. Although the susceptibility of this species to penicillin has decreased, it is sensitive to clindamycin, chloramphenicol, and metronidazole, as well as many of the newer cephalosporins and newer penicillins. *Prevotella disiens* also is isolated regularly from pelvic infections and has a susceptibility pattern similar to that of *P. bivia. Bacteroides* (formerly *Bacteroides fragilis* group) have been identified less commonly in studies but still play an important role. Because members of this group have been recognized by clinicians for their resistance to many antibiotics and their frequent involvement in pelvic and abdominal infections, it is necessary to maintain this connotation for all these species with a simple designation. Thus, in clinical literature, these species commonly are referred to as the *B. fragilis* group. Antibiotics of choice for therapy of *B. fragilis* group infections are metronidazole, imipenem, some penicillin b-lactamase inhibitors, and chloramphenicol. Of the newer cephalosporin-type agents, cefoxitin and cefotetan have the best *in vitro* activity against the *B. fragilis* group (10). Piperacillin, mezlocillin, and related drugs, given in large parenteral doses, also are active against the vast majority of *B. fragilis* species. Similarly, the b-lactamase enzyme blocker agents are active against these organisms. Previously, it was presumed that *Bacteroides* species other than *B.*

fragilis (e.g., *P. bivia, P. disiens, P. melaninogenica*) were susceptible to penicillin. Recently, multiinstitutional studies of *in vitro* susceptibility have noted increasing resistance by the *Prevotella* organisms. Thus, these organisms require antimicrobial therapy similar to that used for *Bacteroides* (*B. fragilis* group), as shown in Table 1.3.

Fusobacterium

Fusobacteria are isolated less frequently than *Bacteroides, Prevotella,* and *Porphyromonas* and usually are involved in polymicrobial infections. They appear to be less virulent than *Bacteroides* and *Prevotella* and are generally susceptible to penicillin, clindamycin, chloramphenicol, metronidazole, and many of the newer penicillins and cephalosporins. *Fusobacterium* organisms have been implicated as important pathogens associated with amnionitis, especially prior to term.

Mobiluncus

The taxonomic position of *Mobiluncus* remains uncertain. The genus *Mobiluncus* is assigned to the family *Bacteroidaceae,* which contains phenotypically similar organisms that are obligate anaerobic Gram-negative rods (straight, curved, or helical). *Mobiluncus* are curved, motile rods that are Gram-variable or Gram-negative. These rods have tapered ends. These organisms (*Mobiluncus curtisii* and *Mobiluncus mulieris*) are associated with bacterial vaginosis and thus may be involved in the adverse complications attributable to bacterial vaginosis.

YEASTS AND ACTINOMYCES

Yeasts are commonly isolated from the vagina. *Candida albicans* is clearly the most common yeast found in vaginal cultures, but other *Candida* species are seen in 10% to 15%. These include *Candida kefyr* (formerly *Candida pseudotropicalis*), *Torulopsis (Candida) glabrata,* and *Candida tropicalis.* In vaginitis, yeasts are commonly identified by direct microscopy of a potassium hydroxide preparation, but culture is helpful in problem cases (11,12). Vaginal candidiasis is treated by a number of topical agents or by oral agents. Although the initial cure rate for vaginal candidiasis is good (80% to 90%), recurrent infection is a problem. New strategies are discussed in Chapter 12. Systemic *Candida* infections in obstetric or gynecologic patients are unusual and limited to those patients who have received protracted antibiotic or immunosuppressive therapy or who have debilitating diseases.

The genus *Actinomyces* is classified between true bacteria and molds. *Actinomyces israelii,* an anaerobic or microaerophilic organism, is a rare cause of pelvic infection, but it has been isolated in pelvic abscesses associated with intrauterine devices. *Actinomyces* organisms are susceptible to penicillin, most cephalosporins, tetracycline, and rifampin.

TRICHOMONADS

Trichomonas vaginalis, a flagellated parasite, is found in vaginal secretions of approximately 6% of women and is responsible for up to one fourth of cases of infectious vaginitis (Table 1.5). As discussed in Chapter 12 and Chapter 19, *Trichomonas vaginalis* has been associated recently with preterm premature rupture

of membranes and preterm labor and delivery. *Trichomonas vaginalis* is commonly detected by direct microscopy of a wet mount of vaginal secretions. These flagellates are larger than white cells and have great motility in fresh preparations. *Trichomonas vaginalis* also may be detected on the Papanicolaou smear, but the reliability of this technique is uncertain. Culture for *T. vaginalis* is more sensitive than the wet mount. Trichomoniasis is treated with metronidazole (Flagyl) or related 5-nitroimidazole derivatives. Because this organism is transmitted sexually, partners also should be treated. Relative resistance to metronidazole has become common. Most cases respond to a higher dose of metronidazole (13).

Mycoplasmas
Mycoplasma hominis
Ureaplasma urealyticum (formerly T-form mycoplasmas)
Mycoplasma genitalium
Viruses
Cytomegalovirus
Herpes simplex virus
Human papilloma virus
Human immunodeficiency virus
Hepatitis B virus
Human parvovirus
Intracellular bacteria
Chlamydia trachomatis
Parasites
Trichomonas vaginalis
Toxoplasma gondii
Yeasts
Candida albicans
Candida (Torulopsis) glabrata
Candida tropicalis
Candida pseudotropicalis (Candida krfyr)
Saccharomyces cerevisiae

TABLE 1.5. OTHER MICRORGANISMS IN INFECTIONS OF THE GENITAL TRACT OR PREGNANCY

MYCOPLASMAS

These cell wall-deficient microorganisms are distinctly different, morphologically and biochemically, from bacteria and L forms (Table 1.5). *Mycoplasma hominis* and *Ureaplasma urealyticum* are isolated with great frequency from the genital tract (13). *Mycoplasma hominis* has been found in blood cultures of women with postpartum fever. It has been isolated commonly in amniotic fluid from patients with intraamniotic infection or those with preterm labor. *Ureaplasma urealyticum* has been implicated in chorioamnionitis, recurrent abortion, infertility, prematurity, and low-birth-weight infants. The role of genital mycoplasmas in causing adverse pregnancy outcomes is controversial and is discussed in detail in Chapter 19.

Culturing of mycoplasmas requires special techniques that are not available in most hospital or commercial laboratories. *Mycoplasma hominis* is susceptible to tetracycline, clindamycin, and lincomycin, whereas *Ureaplasma* organisms are sensitive to tetracycline and erythromycin.

CHLAMYDIA TRACHOMATIS

Chlamydia are intracellular bacteria that are involved in a variety of genital and perinatal infections (14,15). From 2% to 25% of women have positive cervical cultures for *Chlamydia trachomatis* (Table 1.5). Isolation rates of approximately 25%

are found in high-risk groups, such as women attending sexually transmitted disease clinics. Overall, the incidence of cervical infection in the United States probably averages 3% to 6%. In males, chlamydia are responsible for many instances of nongonococcal urethritis. In females, evidence of their virulence has been accumulating. *Chlamydia trachomatis* plays a major role in pelvic inflammatory disease, especially in subsequent tubal obstruction. Newborns may acquire this microorganism from the maternal genital tract. Approximately 40% of infants delivered from an infected mother develop conjunctivitis, and 10% develop late-onset pneumonia. Chlamydia infections are described in detail in Chapter 5. Azithromycin and doxycycline are the antibiotics of choice in treating chlamydial infection, with erythromycin and ofloxacin used alternatively (8). Other effective agents include sulfisoxazole, clindamycin, ofloxacin, and azithromycin. High doses of ampicillin or amoxicillin also appear to provide some cures. In pregnancy, erythromycin base and amoxicillin are recommended, with azithromycin and other erythromycin preparations as alternatives (8).

VIRUSES

Several viruses are commonly found in the female genital tract (Table 1.5). Herpes simplex virus is a well-known cause of an ulcerative, usually self-limited, lower genital tract infection. Herpesvirus also can cause asymptomatic cervical infection. In surveys of adult females, this virus has been isolated from the genitalia in 0.02% to 1%.

Approximately 85% of isolates of herpesvirus in the genital tract are of serologic type 2 (16) and 15% are serologic type 1, which more commonly causes oral lesions. Serologic surveys show that 25% of reproductive age females have serum antibody to herpesvirus type 2 (16). The most reliable method for detecting herpes infection has been culture, but this technique has a recognized false-negative rate. Polymerase chain reaction techniques have been introduced. Clinical diagnosis, Papanicolaou smears, enzyme-linked immunosorbent assay, and monoclonal antibody tests are less reliable. Several drugs are available for treatment or prevention of genital herpes infections (see Chapter 6).

Cytomegalovirus (CMV) is the most common virus found in the female genital tract. It is found in the cervix in 3% of 18% of pregnant women, more commonly in indigent, young, primiparous women. Serologic evidence of past infection is found in 20% to 70% of adults. Genital infections are asymptomatic and occur mainly in seropositive women. CMV may be transmitted vertically to the fetus by transplacental infection. It is estimated that 0.5% to 2.5% of neonates have this congenital infection, but most cases are asymptomatic (17,18). An additional 3% to 5% of newborns acquire CMV during delivery. If a mother has CMV in her genital tract, there is a 30% to 50% chance that her neonate will acquire the virus. CMV can be detected by culture, and several antibody tests are available. Ganciclovir can be used for treatment of CMV infection, but this drug may be toxic (19).

Human papilloma virus (HPV) is the causative agent of genital warts, condylomata acuminata. The recent marked rise in interest in this virus stems from its dramatic increase in frequency and its relationship to genital tract malignancy. The common HPV types are 6, 11, 16, and 18. The first two are more common and usually are associated with benign genital warts; the latter two more likely are associated with higher grades of cervical intraepithelial neoplasia or invasive carcinoma. Treatment

has generally consisted of surgical excision, cryotherapy, chemical burning, or laser vaporization. Recently, treatment with parenterally or locally administered interferon has been successful. Another immune modulator, imiquimod (Aldara), has been approved for treatment. Although the likelihood is small, maternal HPV infection may lead to juvenile-onset respiratory papillomatosis. However, cesarean delivery is not recommended solely on the basis of maternal HPV infection (20).

Other viruses that cause nongenital infections may have the genital tract as a portal of entry. Among these are human immunodeficiency virus, the causative agent in acquired immunodeficiency syndrome (AIDS), and hepatitis B virus. Hepatitis and AIDS are discussed in detail in Chapter 9 and Chapter 10, respectively. Other viruses cause adult systemic infection that may have serious fetal sequelae if the infection occurs in pregnancy (see Chapter 16).

CHANGES IN VAGINAL MICROFLORA

One should not conclude from this description of vaginal microflora that it is a static situation. Certainly, there are vast differences in flora between different groups of women and interesting shifts from time to time in the flora of one particular woman.

Age

At birth, the vagina is sterile. Secondary to maternal estrogen effect, lactobacilli growth is enhanced for a short time. The estrogen effect is gone within several weeks, and lactobacilli disappear until the onset of puberty, when, under the influence of endogenous estrogen, the vaginal flora becomes dominated by lactobacilli. It is suggested that postmenopausal women have a decrease in *Lactobacillus* colonization, but that treatment with estrogens results in a higher rate of recovery of lactobacilli and probably of diphtheroids. Thus, there seems to be an important interaction between vaginal colonization and hormonal milieu. Changes associated with aging have been reported in other groups of bacteria, but the conclusions are less uniform.

Sexual Activity

Sexual intercourse leads to changes in lower genital tract microorganisms, mainly sexually transmitted ones. In addition to introducing major pathogens such as *N. gonorrhoeae, C. trachomatis,* and herpesvirus, intercourse leads to increases in genital mycoplasmas.

Contraception

Use of oral contraceptives appears to have minimal effect on the vaginal ecosystem. On the other hand, use of intrauterine contraceptive devices increases the number of anaerobic bacteria in the cervix and augments the risk for bacterial vaginosis, thus increasing the risk for pelvic inflammatory disease.

Pregnancy And Delivery

A number of studies have suggested that there is a progressive increase in

colonization by *Lactobacillus* organisms during pregnancy, but changes in other bacterial groups are not well established. After delivery, dramatic changes in vaginal flora occur. There are marked increases in anaerobic species by the third postpartum day. Possible predisposing features to anaerobic vaginal colonization in postpartum women include trauma, presence of lochia and suture material, examinations during labor, and changes in hormonal levels. By the sixth week postpartum, the vaginal flora is restored to a normal distribution.

Surgery

Major procedures, such as hysterectomy, lead to wide changes in vaginal flora, including decreases in lactobacilli and diphtheroids and increases in aerobic and anaerobic Gram-negative rods (predominantly *E. coli* and various *Bacteroides* [*Prevotella*]). In addition, most investigators have noted a further shift when prophylactic or therapeutic antibiotics are used. As expected, use of antibiotics results in a decrease in susceptible flora and a corresponding increase in resistant organisms.

Homeostasis

Homeostatic mechanisms have been identified that function to maintain the stability of the normal vaginal flora (21). Production of hydrogen peroxide by certain *Lactobacillus* species appears to play a crucial role in maintaining the normal vaginal ecosystem. In addition, the low pH (acidity) of the normal vagina protects against exogenous organisms. Antimicrobial agents can disrupt the normal vaginal ecosystem, especially if they eliminate the hydrogen peroxide-producing lactobacilli.

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2

USE OF THE MICROBIOLOGY LABORATORY IN INFECTIOUS DISEASES

The role of the microbiology laboratory in the clinical care of obstetric and gynecologic patients with infection has been affected by a variety of factors (1). First, the introduction of potent antimicrobial agents with their dramatic favorable impact on mortality due to infection in obstetrics and gynecology has lulled clinicians into complacency. Second, the trend to centralize laboratory facilities has made it difficult for (a) clinicians to work with laboratory personnel; (b) the central microbiology laboratory to meet the needs for obtaining and transporting specimens; and (c) the laboratory to recover and identify the tremendous variety of microorganisms now recognized to be human pathogens. Third, as academic microbiology departments have focused on basic research involving molecular biology, medical students and house officers often complete their training with a minimal background in clinical microbiology and infectious disease. Fourth, formal organized instruction in clinical and laboratory diagnosis and management of sexually transmitted diseases (STDs) is an often-neglected area of the medical school curriculum and house officer training. Fifth, the virtual explosion in knowledge and technology related to the field of microbiology has widened the gap between the reality of microbiology laboratory capabilities and the clinician's understanding of these capabilities and their application to patient care. In particular, the introduction of more sensitive, rapid, and cost-efficient diagnostic tests, such as enzyme-linked immunosorbent assay (ELISA), DNA hybridization techniques, monoclonal antibody techniques, and nucleic acid amplification techniques, has resulted in a shift from the use of classic microbiologic isolation and identification of microorganisms to methods that rely on advances in molecular biology. Last, diagnostic virology has now entered the mainstream of clinical practice (2).

This chapter will review the role played by microbiology and diagnostic molecular biology laboratories in clinical medicine. A description of the proper collection, handling, and transport of specimens is presented, with emphasis on the important role clinicians must take in providing laboratories with appropriate specimens in a timely manner so that laboratories can provide quality testing. The clinical application of recently developed molecular-based tests for STDs and other pathogens will be

addressed.

Figure 2.1 provides an overview of the types of methods used for the diagnosis of infectious agents. The specific methods and relative usefulness of the tests are dependent on the microorganism(s) being sought (3).

FIGURE 2.1. Methodologies used for the diagnosis of infectious agents. (Reprinted with permission from ref. 3.)

The continuous and rapid increase in knowledge and technology of microorganisms, the immune response to these organisms, and their molecular biology has exploded during the last 2 decades. The introduction of more sensitive and specific diagnostic tests, such as ELISA, *in situ* nucleic acid hybridization, and molecular assays [e.g., probes and nucleic acid amplification such as polymerase chain reaction (PCR) and ligase chain reaction (LCR)], has resulted in the evolution of tests from the classic microbiological practices of isolation on bacteriologic agar or for viruses in tissue culture. The past decade has resulted in explosive growth in the application of molecular biology to the diagnosis of infection. New organisms that could never be grown are being identified and their role in human infection is being demonstrated (e.g., hepatitis C virus, *Helicobacter pylori*).

The basic purpose of the infectious disease laboratory is to identify microorganisms that cause clinical disease. As noted by Gill et al. (3), a critical component in elucidating the etiologic agent(s) in infections is a partnership and active communication that involves the clinician and the microbiology laboratory. The laboratory must be capable of handling a wide variety of specimens that come from a multitude of clinical infection sites and thus require a diversity of collection and transport systems (4,5). Physicians refer to the laboratory to obtain assistance in the diagnosis and treatment of infectious diseases, but they also expect the laboratory to (a) produce reliable, rapid, and clinically useful facts; (b) establish and maintain a consistent reporting system; (c) provide specific and concise guidelines for proper specimen collection, handling, and transport; (d) initiate interpretive reporting for unusual microorganisms, normal flora, and monitoring of the therapeutic response; and (e) provide susceptibility data that will guide therapeutic decisions.

Clinicians should realize that laboratory results are only as good and as useful as the

specimens received by the laboratory. The physician must provide the infectious disease laboratory with pertinent patient information, perform appropriate specimen collection, ensure proper and prompt specimen transport to the laboratory, and request isolation or identification of suspected pathogenic organisms.

Each microorganism has its own requirements for collection, handling, transport, growth, isolation, and detection in the laboratory. Clinics and laboratories throughout the world have variable capabilities for isolating microorganisms, such as anaerobic bacteria, *Chlamydia trachomatis,* mycoplasmas, ureaplasmas, and viral pathogens, which require sophisticated technology and experienced laboratory personnel. For example, in a study of chlamydia culture from the cervix, Schachter et al. (6) found that sensitivity varied from 51.8% to 92.0% among a series of five laboratories throughout the United States. Clearly, the accuracy of a laboratory's results for specific organisms varies according to its focus, expertise, and personnel.

General guidelines for collection of clinical specimens from infected patients has been summarized by Gill et al (3). Specimen selection must be based on the characteristics of suspected infectious agents. The clinical specimen should be obtained from the site of infection and be representative of the infectious process. An adequate quantity of material is required for the laboratory to perform a complete evaluation. The clinician must be scrupulously careful to avoid contamination of the specimen by microorganisms indigenous to skin and/or mucous membranes (i.e., oral cavity, vagina, or bowel). Once a suitable specimen is obtained, it should be forwarded promptly to the laboratory. Finally, it is crucial that, whenever possible, specimens for culture be obtained before institution of antimicrobial therapy. Table 2.1 summarizes the general guidelines for specimen collection and transport of common specimens from obstetric and gynecologic infections. Recent advances in the use of molecular diagnostic techniques for the diagnosis of infectious diseases have revolutionized the laboratory diagnosis of these infections and added another approach to the traditional use of stain, culture, and serology for diagnosing infectious agents (3).

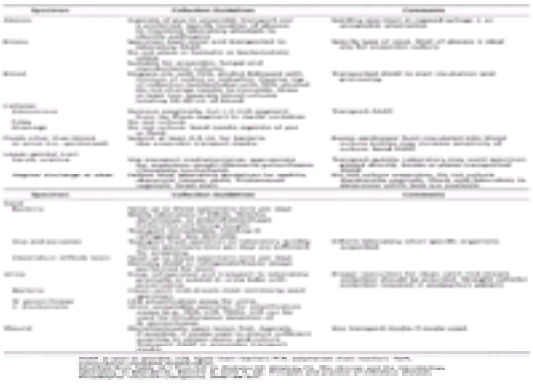


TABLE 2.1. GUIDELINES FOR COLLECTION AND TRANSPORT OF COMMONLY OBTAINED SPECIMENS IN INFECTIONS OF THE FEMALE GENITAL TRACT

PRINCIPLES OF DIAGNOSTIC MOLECULAR MICROBIOLOGY

In 1980, Moseley et al. (7) reported the first clinically useful application of recombinant DNA technology to the diagnosis of an infectious disease using DNA–DNA hybridization in stool samples spotted on filters to detect enterotoxigenic *Escherichia coli.* The following decade resulted in the availability of DNA probes for the identification of bacterial, viral, fungal, parasitic, and helmintic pathogens (8,9).

Nucleic acid probes are segments of DNA or RNA that are labeled with enzymes, antigenic substrates, chemiluminescent moieties, or radioisotopes and can bind with high specificity to complementary nucleic acid sequences from the microorganism of interest (3,9). Oligonucleotide probes are probes with less than 50 base pairs. They can be synthesized and purified commercially and hybridize more rapidly than layer probes. Probe technology uses the presence of nucleotide sequences unique to a given organism or species as a molecular fingerprint for identification (10). Probes can be developed that identify organisms grown in culture (culture confirmation assays) or detect and identify organisms directly in clinical samples.

Several nucleic acid amplification techniques have been developed. These include PCR, LCR, self-sustaining sequence replication (3SR), strand displacement amplification (SDA), and QB replicase. Nucleic acid amplification methods include three general categories: (i) target amplification (PCR, 3SR, or SDA); (ii) probe amplification systems (LCR or QB replicase); and (iii) signal amplification where the signal generated from each probe molecule is increased by using compound probes or branched-probe technology (3,11). PCR involves three steps: (i) DNA or target organism is denatured to a single strand; (ii) two primers (single-stranded DNA 20 to 30 bases in length) bind to regions of DNA flanking the target sequence to be amplified; and (iii) the DNA between the two primers is reproduced. With each round of PCR, the target DNA equence increases by a power of two. At the end of 30 replication cycles, over a million-fold amplification of the target DNA has taken place. Nested PCR is a modification of PCR in which a first round of amplification is performed with a single primer for 15 to 30 cycles, followed by a second round using a second primer specific for the internal sequence amplified by the first primer. This approach leads to very high sensitivity.

Nucleic acid hybridization requires that two molecules of single-stranded DNA meet and form a stable double-stranded molecule (12). Both DNA probe and amplification techniques are based on this technology (9). Hybridization can be accomplished using solution phase hybridization or solid phase hybridization. Although solid phase hybridization is somewhat less sensitive, it greatly facilitates the handling of multiple specimens (9). An important type of solid phase hybridization is *in situ* hybridization, in which whole cells or tissue sections affixed to microscopic slides are assayed by hybridization.

A variety of commercially available probe kits have become available (Table 2.2). These include probes for (i) STD organisms such as *C. trachomatis* and *Neisseria gonorrhoeae*; (ii) respiratory pathogens such as *Mycobacterium* sp, including *Mycobacterium tuberculosis,* and *Legionella* sp; (iii) Gram-positive organisms such as *Streptococcus pneumoniae, Staphylococcus aureus,* group B streptococci, enterococci, and *Listeria monocytogenes*; and (iv) Gram-negative organisms such as *Haemophilus influenzae, E. coli*, and thermophilic campylobacters (10). The initial

assays were based on hybridization with DNA probe technology to detect specific ribosomal RNA (Gen-Probe system). Currently this system uses acridinium ester-labeled, single-stranded DNA probes to detect complementary ribosomal RNA sequences of the target organism. This reaction is measured using chemiluminescence, which is read on a luminometer (3). Only a few organisms, primarily *C. trachomatis* and *N. gonorrhoeae*, are detected directly using probe technology. More commonly this method is used for culture confirmation of organisms such as fungi and mycobacterial species (3).

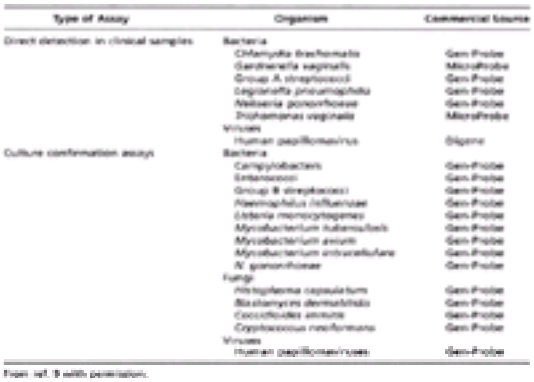


TABLE 2.2. EXAMPLES OF COMMERCIALLY AVAILABLE PROBES

Polymerase chain reaction technology has been applied rapidly to the detection of microorganisms directly from clinical samples (2,3,11,13,14 and 15). Among the agents for which PCR is used are the DNA viruses, including herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, parvovirus B19, human herpes virus type 6, human papillomavirus, hepatitis B virus, and polyomavirus (Table 2.3). Inclusion of an initial reverse transcriptase step that converts RNA into DNA permits PCR detection of RNA-containing viruses such as human immunodeficiency virus (HIV) types 1 and 2, human T-cell lymphotrophic virus type I, enterovirus, hepatitis C virus, and rotavirus. PCR assays for bacterial also have been developed (Table 2.4). Examples of bacterial organisms for which PCR technology has been introduced include *C. trachomatis, M. tuberculosis, Borrelia burgdorferi, Legionella pneumophila, and Bacteroides fragilis* (10,14,15).

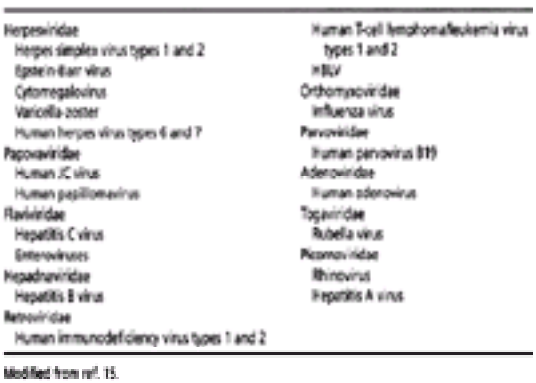


TABLE 2.3. VIRAL PATHOGENS DETECTED BY NUCLEIC ACID AMPLIFICATION

Mycobacterium sp.
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Chlamydia trachomatis
Borrelia burgdorferi
Mycoplasma fermentans
Salmonella typhimurium
Legionella typhimurium
Clostridium difficile
Treponema pallidum
Enterotoxigenic *Escherichia coli*
Shigella sp.
Chlamydia pneumoniae
Staphylococcus aureus
Whipple disease-associated bacterium
Helicobacter pylori
Listeria monocytogenes
Ureaplasma urealyticum
Neisseria gonorrhoeae
Mycoplasma genitalium
Haemophilus influenzae

Modified from ref. 15.

TABLE 2.4. BACTERIAL PATHOGENS DETECTED BY NUCLEIC ACID AMPLIFICATION

DNA ligase-dependent amplification (LCR) is an alternative nucleic acid probe amplification technique that is based on target-dependent ligation of oligonucleotide probes (16). Rather than using polymerase to copy genetic information, LCR uses DNA ligase to join two pairs of complementary oligonucleotide probes after they have bound to a target sequence. After the two probes have been ligated, the product, which mimics one strand of the original target sequence, serves as a template for ligation of complementary oligonucleotides. The components then are heated to denature the template and allowed to anneal to new probes at a lower temperature (16). Originally, fresh DNA ligase had to be added at the end of each round, which made the process cumbersome. Recently, the use of thermophilic DNA ligase, which remains active during the thermal cycling steps, has greatly simplified the LCR test (3,11). Ligase chain reaction has been used to detect microorganisms including *N. gonorrhoeae, C. trachomatis, B. burgdorferi,* and *Mycobacterium* sp (15).

Several additional amplification methods have been developed (11). Self-sustaining sequence replication uses the collective activities of three enzymes to isothermally amplify an RNA target. Up to 10 million-fold amplification occurs within a 1- to 2-hour incubation (11). Strand displacement amplification is an isothermal DNA amplification method using specific primers, a DNA polymerase, and a restriction endonuclease to produce exponential amplification of the target (11). It can be applied to either single- or double-stranded DNA. Transcription-mediated amplification (TMA) is an isothermal technique that amplifies rRNA target. The QB replicase method is a probe amplification technique that uses incorporation of a single-stranded oligonucleotide probe into an RNA molecule that can be amplified exponentially after target hybridization by the enzyme QB replicase (3).

Detection And Identification Methods

Figure 2.1 outlines the various approaches available for the diagnosis of agents causing infectious diseases. Microorganisms can be identified in patient specimens by either direct detection or culture (3).

Microscopy can be used to detect microorganisms that have been stained directly in patient specimens. The Gram stain is the most commonly used direct stain; it is simple, reliable, and inexpensive. It provides preliminary information as to Gram-positive versus Gram-negative bacteria and rod versus coccus. In the hands of an experienced technician, the Gram stain can serve as a quality control tool for the adequacy of the specimen and accuracy of cultures. However, the Gram stain is nonspecific, and its sensitivity is limited by the amount of material that can be reviewed on a slide (3). Direct fluorescent antibody (DFA) stains have been used for some organisms (*C. trachomatis, Legionella*, some parasites), but their use is limited by inadequate sensitivity when too few organisms are present and the need to be performed by experienced, trained personnel. Wet mounts traditionally are used to look for yeast [potassium hydroxide (KOH)] and *Trichomonas vaginalis* (saline preparation). Many laboratories are using a calcofluor white stain for fungi (3). Although more sensitive, it requires a fluorescence microscope. Wet mounts also are used to detect the presence of “clue” cells as an aid in diagnosing bacterial vaginosis.

Direct antigen detection of patient specimens is now very common and available for a wide variety of microorganisms (3). Antigen detection tests fall into two major categories: latex agglutination and enzyme immunoassay (EIA) (Table 2.5). Antigen detection tests are simple and rapid to perform; those with good sensitivity and specificity, as listed in Table 2.5, have been widely used by clinical laboratories (3).

Latex Agglutination	Enzyme Immunoassay
Bacterial antigens*	Bacterial antigens
Group B streptococci	Group A streptococci
Haemophilus influenzae type b	*Legionella pneumophila* serotype 1
Streptococcus pneumoniae	
Neisseria meningitis	Bacterial toxins
	Clostridium difficile
	Shiga-like toxin of *Escherichia coli*
Fungal antigen	
Cryptococcus neoformans	
	Fungal antigen
	Cryptococcus neoformans
	Parasitic antigens
	Giardia lamblia
	Cryptosporidium parvum
	Entamoeba dispar/histolytica
	Viral antigens
	Adenovirus 40/41
	Herpes simplex
	Influenza A
	Respiratory syncytial virus
	Rotavirus
	Chlamydial antigen
	Chlamydia trachomatis

*Primarily used for cerebrospinal fluid specimens.

Modified from Table 14-6 from Gill VJ, Pedraza DP, Witebsky FG. The clinician and the microbiology laboratory. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone, 2000:184-204.

TABLE 2.5. DIRECT ANTIGEN DETECTION TESTS USED COMMONLY IN CLINICAL PRACTICE

Molecular-based assays were described previously in the section on Principles of Diagnostic Molecular Microbiology. Briefly, these include (i) DNA probe technology to

detect specific ribosomal RNA (Gen-Probe), and (ii) amplification techniques such as PCR, LCR, and TMA. Generally, the sensitivity of DNA probes is equivalent to that of good EIA tests and amplification techniques are more sensitive, thus requiring the presence of a smaller number of microorganisms (3). The use of molecular diagnostics has expanded the ability of microbiology laboratories to detect organisms present in very low quantities, organisms that are difficult or slow to grow, and infectious agents as yet “undiscovered” (3).

Traditionally, diagnostic bacteriology was based on the growth of microorganisms on appropriate culture media and identification based on biochemical characteristics (3). Enriched all-purpose media such as blood or chocolate agar, which grow most ordinary bacterial pathogens, are used for common specimen types. For specimens from lower and upper genital tract infections, which often contain mixed microbial flora, additional plates such as MacConkey or eosin-methylene blue agar for Gram-negative bacteria, phenylethyl alcohol agar for Gram-positive bacteria, kanamycin-vancomycin laked blood agar for *Prevotella* sp, and *Bacteroides* bile esculin for *B. fragilis* group are inoculated (3). Broth media such as thioglycolate, brain-heart infusion, or trypticase soy are used as a backup because a large aliquot of specimen can be inoculated, allowing detection of small numbers of organisms. Once colony growth is detected, Gram-stain morphology, colony size, color, shape, presence or absence of hemolysis, and biochemical reactions are used to identify bacteria (3).

Antimicrobial Susceptibility Testing

In general, susceptibility testing of pathogens is indicated when the response of the organism is not predictable (3). The increasing occurrence of resistance among bacteria has resulted in more species requiring susceptibility testing (3). The National Committee for Clinical Laboratory Standards (NCCLS) has published standards related to bacterial susceptibility testing (17,18,19 and 20). Use of these NCCLS criteria permits testing and reporting of results for nearly all the more common and nonfastidious bacteria (3).

As reviewed by Finegold et al. (21), susceptibility testing of anaerobic bacteria has been controversial but is warranted, because anaerobes are significant pathogens and their susceptibility patterns are not predictable. Most clinical microbiology laboratories do not perform routine susceptibility testing of anaerobic bacteria. The NCCLS recommends that susceptibility testing of anaerobic bacteria be performed in certain clinical settings, such as brain abscess, endocarditis, osteomyelitis, prosthetic device infection, and refractory or recurrent bacteremia (20,22). The recommended procedures for susceptibility testing of anaerobes are agar dilution testing, microbroth dilution, and macrobroth dilution (21). The broth disk elution method, which was the simplest and most commonly used method, is no longer recommended by the NCCLS. An interesting alternative, the epsilometer (E-test), has been shown to be a promising test for anaerobic bacteria susceptibility testing (23).

On the other hand, susceptibility testing of aerobic bacteria is widely performed by clinical microbiology laboratories. The laboratory must test and report those antimicrobial agents that are most appropriate for the infection site and the organism(s) isolated (24). In addition, the agents tested should be those that are on the hospital formulary (24). The macrodilution or tube dilution method was one of the

first antimicrobial susceptibility testing methods introduced. Miniaturization and mechanization of this method resulted in “microdilution” susceptibility testing, which is the most common method used by clinical laboratories for susceptibility testing (24). This method uses plastic disposable microtiter trays containing 96 wells, which provide for 12 antibiotics to be tested in a range of 8 twofold dilutions in a single tray. The second most commonly used method for testing susceptibility of aerobic bacteria is the disk diffusion or Kirby-Bauer test (17). Antibiotic-containing filter paper disks are placed on an inoculated agar plate and the zones of growth inhibition around the disks are measured. These results are compared to the zone size interpretive criteria published by the NCCLS (17) or the U.S. Food and Drug Administration (drug package insert data). Agar dilution testing is an additional but cumbersome method (24). Its major advantage is its ability to test fastidious organisms that do not grow well in broth (e.g., *N. gonorrhoeae*). In addition, it provides a quantitative result [minimum inhibitory concentration (MIC)].

The MIC is the lowest concentration of an antimicrobial agent that inhibits growth of the test microorganism. The minimal bactericidal concentration (MBC) is the lowest concentration of an antimicrobial agent that kills the test microorganism. The NCCLS has published definitions of susceptible, intermediate, and resistant (19). Susceptible implies that an infection due to the test organism may be treated appropriately with the recommended dosage of an antimicrobial agent for that type of infection and infecting bacteria. The intermediate category identifies isolates with MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. The intermediate category implies clinical usefulness in body sites where the drug is physiologically concentrated (e.g., quinolones and b-lactams in urine) or when a high dosage of antimicrobial agent can be used (e.g., b-lactams). Resistant strains are not inhibited by usually achievable systemic concentrations of the antimicrobial agent using normal dosage schedules and/or fall in the range in which specific microbial resistance mechanisms are likely (e.g., b-lactamase enzymes) and clinical efficacy has not been reliable in treatment trials.

Serology

Serology is useful for diagnosing infectious diseases that are caused by microorganisms that are not easily or quickly recovered by culture. There are two basic approaches to serologic testing: antigen detection and antibody detection. Antigen detection is generally rapid and accurate. It is performed on a specimen of infected tissue (biopsy or body fluid). Antigen detection is useful for many pathogens that are difficult or impossible to culture in the laboratory. Examples include *C. trachomatis*, HSV, rotavirus, HIV, Legionnaires disease, and syphilis. Monoclonal antibody technology has stimulated a tremendous explosion of current investigative efforts, and several antigen detection systems have become available (e.g., *C. trachomatis*, HIV).

Serologic tests based on antibody detection (Table 2.6) generally are slower and less precise than those based on antigen detection. There are frequent cross-reactions between antibodies of the various organisms. A single specimen that measures immunoglobulin M (IgM) antibody may be diagnostic. However, most available tests measure immunoglobulin G (IgG) and thus cannot differentiate past from present infection. A convalescent specimen is obtained 14 to 21 days after the initial specimen and must show a fourfold rise in antibody titer as an indicator of

acute infection.

Single Specimen Usually Adequate	Paired Specimens Usually Required
Amoebic liver abscess	Mycoplasma pneumonias
Brucellosis	Chlamydial diseases
Coccidioidomycosis	Meningoencephalitis
Echinococcal cyst	Cytomegalovirus
Hepatitis A (IgM)	Histoplasmosis
Hepatitis B (IgM and anti-HBcAg)	Legionnaires disease
Anti-Hepatitis B	Rubeola
Human immunodeficiency virus	
Malaria	Mumps
Epstein-Barr virus mononucleosis	Rickettsial disease
Group A β-hemolytic streptococci	Rubella
Trichinosis	Tularemia
Neonatal chlamydia pneumonia	Yellow fever

TABLE 2.6. INFECTIOUS DISEASES COMMONLY DIAGNOSED BY ANTIBODY RESPONSE

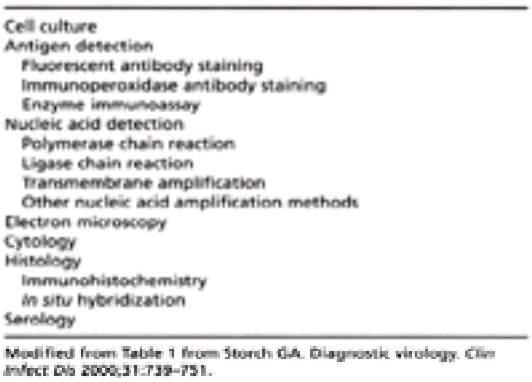
Use of serology in the diagnosis of syphilis is fully described in Chapter 7. Initial evaluation involves the use of nontreponemal tests [Venereal Disease Research Laboratories (VDRL), rapid plasma reagin (RPR)]. They are nonspecific and are associated with many false-positives. The major clinical use of the nontreponemal tests is screening, because the tests are quick and inexpensive. Quantitative titers can be used to evaluate therapy. Confirmation of the screening tests for syphilis requires use of specific treponemal tests. The fluorescent treponemal antibody-absorption (FTA-ABS) test is the most commonly used confirmatory test for syphilis. However, it is expensive and technically difficult. The microhemagglutination–*Treponema palladium* (MHA-TP) assay is easier to perform and less expensive. It has replaced the FTA-ABS test in many centers.

The use of serology for diagnosis of HIV infection is discussed fully in Chapter 10, for the genital mycoplasmas in Chapter 4, and for HSV in Chapter 6.

Diagnostic Virology

In 2000, Storch (2) reviewed the diagnostic approach to clinically important viral infections. He noted that diagnostic virology is rapidly entering into the mainstream of clinical medicine. Several recent advances and/or developments contributed to this emergence of diagnostic virology, including the following. (i) Dramatic progress in antiviral therapy has increased the need for specific viral diagnoses. (ii) Technologic developments, especially molecular diagnostics, have provided new tools for viral diagnosis. (iii) The HIV/acquired immunodeficiency syndrome epidemic has led to a greater number of patients at risk for opportunistic viral infections. (iv) Modern management of HIV infection and hepatitis C has provided a new paradigm for using molecular techniques in the management of chronic viral infections (2). Multiple methods are available for the laboratory diagnosis of viral infections, including viral culture, antigen detection, nucleic acid detection with or without amplification, and

serology (Table 2.7) (2).



Cell culture
Antigen detection
Fluorescent antibody staining
Immunoperoxidase antibody staining
Enzyme immunoassay
Nucleic acid detection
Polymerase chain reaction
Ligase chain reaction
Transmembrane amplification
Other nucleic acid amplification methods
Electron microscopy
Cytology
Histology
Immunohistochemistry
In situ hybridization
Serology

Modified from Table 1 from Storch GA. Diagnostic virology. Clin Infect Dis 2000;31:739–751.

TABLE 2.7. TECHNIQUES USED IN DIAGNOSTIC VIROLOGY

Cell culture has been the traditional mainstay of diagnostic virology. With the introduction of new molecular technologies, the relative importance of viral isolation has diminished significantly (2). However, viral culture remains necessary to provide viable isolates for characterization, such as phenotypic antiviral susceptibility testing (2). Herpes simplex virus is the virus for which culture is most useful (2). Viral culture also is used to detect CMV, varicella-zoster virus, adenovirus, respiratory syncytial virus, influenzae and parainfluenzae viruses, rhinovirus, and enterovirus. However, rapid antigen detection and nucleic acid amplification detection are replacing viral culture for these viruses (2).

Antigen detection methods for viral agents include fluorescent antibody staining, immunoperoxidase staining, and EIA. For diagnostic virology, fluorescent antibody staining is the most commonly used antigen detection method (2). The most important viruses identified by antigen detection methods include (i) respiratory syncytial virus, influenzae and parainfluenza viruses, and adenoviruses in respiratory specimens; (ii) HSV and varicella-zoster virus in cutaneous specimens; (iii) rotavirus in stool specimens; and (iv) CMV and hepatitis B virus (hepatitis B surface antigen [HBsAg]) in blood (2).

The advent of PCR analysis made possible the diagnosis of viral infection using sensitive detection of specific viral nucleic acids (2). Potentially any virus can be detected using this technology. PCR analysis has been adapted to detect viral RNA by including the use of the enzyme reverse transcriptase. Quantitative nucleic acid detection techniques are available to assess the viral load of HIV and hepatitis C virus. Multiplex PCR can be used to simultaneously detect multiple infectious agents in a single specimen, such as from a genital ulcer. Nucleic acid amplification assays include target amplification (e.g., PCR, LCR, and TMA) or signal amplification assays (e.g., branched-chain DNA assay and hybrid capture assay) (2).

Detection of specific antiviral antibodies is a traditional method for diagnosis of viral infections. However, in most instances, the need for acute and convalescent antibody titers has limited the clinical usefulness of serologic diagnosis of viral

infection (2). Detection of virus-specific IgM antibodies can diagnose with a single specimen many viral infections, including EBV, CMV, hepatitis A virus, hepatitis B virus (IgM antibody to hepatitis B core antigen), parvovirus B19, measles, rubella, mumps, and arbovirus (2). Serologic testing is useful in chronic infections, such as HIV, where antiviral antibodies always indicate current infection, and hepatitis C virus, where antibodies usually (85%) indicate current infection (2). Serology also is useful to determine immunity to viruses such as varicella-zoster virus, CMV, EBV, HSV, measles, rubella, parvovirus B19, hepatitis A, and hepatitis B (anti-HBsAg).

Infections Of The Lower Female Genital Tract

The clinically important bacterial infections of the lower genital tract in women fall into four major categories (Table 2.8).

Infection	Etiologic Agent
Urethritis	*Neisseria gonorrhoeae* (GC)
	Chlamydia trachomatis (CT)
Cervicitis	*N. gonorrhoeae*
	C. trachomatis
	Herpes simplex virus
Vaginitis/vaginosis	*Trichomonas vaginalis*
	Candida albicans
	Gardnerella vaginalis
	Anaerobic bacteria
Vulvitis	Herpes simplex virus
	C. albicans

TABLE 2.8. CAUSATIVE AGENTS IN LOWER GENITAL TRACT INFECTION IN WOMEN

Diagnosis of urethral infections caused by *N. gonorrhoeae* can be made on a slide obtained from a direct smear and stained with methylene blue or Gram stain. Methylene blue is quicker and as accurate as the Gram stain for identifying the typical intracellular diplococci of gonococcus (GC). To obtain an appropriate urethral specimen, a sterile calcium alginate swab (Calgiswab) is inserted 2 to 3 cm into the urethral orifice, gently twirled slowly, and allowed to remain for 10 to 15 seconds. Direct smears for GC from the urethra have a high degree of sensitivity and specificity (11,25). Direct smear with Giemsa straining for detection of *C. trachomatis* intracellular inclusions can be used with conjunctivitis, but this technique is not appropriate for genital tract specimens. Use of PCR and LCR on female urine specimens for GC has not been the object of any serious study. Studies using urine from symptomatic and asymptomatic chlamydia-infected women have demonstrated the effectiveness of PCR and LCR technology for detecting *C. trachomatis* (26,27,28,29,30,31,32,33,34 and 35).

In females with symptoms and/or signs of urethritis, GC specimens should be obtained for culture from the urethra, and urine cultures should be obtained to rule out the presence of a urinary tract infection (UTI). Isolation of *N. gonorrhoeae*

requires careful specimen collection and handling by the clinician using an enriched bacteriologic medium, high humidity, appropriate incubation temperature, and CO_2 tension for optimal growth. The most common selective media is modified Thayer-Martin medium, which contains vancomycin, colistin, nystatin, and trimethoprim to prevent growth of fungi and non-*Neisseria* bacteria. Alternative selective media are Martin-Lewis and New York City media (11). The urethral swab is streaked directly onto the selective media using a "Z" format. The swab is rolled over the agar to adequately distribute the microbe on the swab onto the media, then the culture is incubated immediately in a CO_2 incubator or candle jar. Cultures should be held overnight at 35°C ± 1°C before transport to the laboratory to establish adequate *Neisseria* growth. Shipment of specimens before overnight incubation can lower the sensitivity of GC culture by 50%. The agar plates are examined daily for 3 days. Visible colonies are Gram stained to identify Gram-negative diplococci and then tested for oxidase production to confirm the presence of *N. gonorrhoeae.* Other commercially available transport media and systems, such as Transgrow, Amies, Neigon, MICROCULT, or JEMBEC, can be used, but their sensitivity is less than that of Thayer-Martin medium unless they reach the laboratory rapidly (less than 24 hours) (25,36).

Culture of chlamydia from the urethra of women can be achieved readily if the requisite specimen collection materials are available, along with an appropriate cold chain leading from the patient to the testing laboratory. Thin, 2- to 3-cm Dacron urethral swabs introduced 2 to 3 cm into the female urethra for 10 to 15 seconds must obtain cellular material, as *C. trachomatis* is an obligate intracellular organism. These swabs are added immediately to a suitable chlamydial transport medium (2SP) that is refrigerated at 4°C or kept on wet ice for transport to the laboratory. Chlamydia culture specimens must reach the infectious disease laboratory within 24 hours of collection, whereupon aliquots can be cultured at once or the entire specimen, containing the swab, can be frozen at –80°C for storage. Chlamydial culture has been replaced to a large extent by antigen detection or nucleic acid amplification methods (Table 2.9). Quinn and coworkers (37) demonstrated that direct immunofluorescence staining (MicroTrak) of urethral specimens had sensitivity of 100%, specificity of 99%, and positive predictive value of 82%. An alternate technique for detecting chlamydial antigens is the use of an immunoassay (Chlamydiazyme). This EIA-type test has been shown to have sensitivity of 81% to 89% and specificity of 90% to 98% (38,39). Polymerase chain reaction amplification of urethral specimens from women attending an STD clinic in Pittsburgh, Pennsylvania, revealed that 35 patients (13.7%) were positive and that, of these 35 women, only 21 (60%) were positive for chlamydia in the cervix (40). Of all the women with urogenital chlamydial infections, chlamydia was identified using PCR in both the cervix and urethra in 52.5% of patients, 35% were positive in the urethra only, and 12.5% were infected solely in the cervix. These data suggest that routine screening for chlamydia infections in women should include an urethral specimen, as well as an endocervical specimen.

Investigator	Reference	Year	Sensitivity of Culture	Sensitivity of Enzyme Immunoassay	Sensitivity of Polymerase Chain Reaction
Wiesenfeld et al.	40	1994	ND	61.5%	89.7%
Vogels et al.	33	1993	84.4%	NA	96.9%
Bass et al.	34	1993	86%	NA	96.5%
Loeffelholz et al.	35	1992	85.7%	58.8%	97%

NA, not available; ND, not determined.

TABLE 2.9. STUDIES COMPARING CHLAMYDIA CULTURE, POLYMERASE CHAIN REACTION, AND ENZYME IMMUNOASSAY IN SPECIMENS FROM THE ENDOCERVIX

Cervicitis now is recognized to be a distinct clinical entity, and mucopurulent cervicitis (MPC) has been described as analogous to male urethritis (41). The clinical criteria for MPC are presence of mucopurulent discharge from the endocervix, and erythema, edema, and friability of the cervix. The two major etiologic agents of MPC are *N. gonorrhoeae* and *C. trachomatis.* Unlike urethral specimens, direct smears for *N. gonorrhoeae* from the cervix lack specificity and sensitivity. Diagnosis of *N. gonorrhoeae* infection of the cervix from symptomatic or asymptomatic patients requires isolation and identification of GC by culture, followed by identification using Gram staining and oxidase production. A single endocervical swab will result in recovery of approximately 90% of *N. gonorrhoeae*-infected women; two consecutive endocervical swabs or an endocervical plus an anal culture swab will recover 99% of *N. gonorrhoeae*-infected women. Thus, we recommend the use of two swabs that can be plated onto the same Thayer-Martin culture. Culture remains the “gold standard” for diagnosis of cervical and urethral gonorrhea, but in clinical practice it is rapidly being replaced by molecular diagnostic methods (3,11), particularly DNA hybridization (probe) assays such as PACE 2 (Gen-Probe, San Diego, CA) (42).

Establishing chlamydia infections in women has progressed historically from tissue culture isolation to antigen detection tests (DFA, EIA) to nucleic acid amplification (PCR, LCR, TMA). Isolation of *C. trachomatis* in tissue culture shell vials, microtiter plates, or 24-well tissue culture plates requires the use of a cell culture line (usually cycloheximide-treated McCoy cells), where monolayers of cells are inoculated (using centrifugation) with the chlamydia transport medium containing a swab from either the urethra and/or endocervix. Identification of chlamydia-infected cells is conducted after 48 to 72 hours using a fluorescein-labeled monoclonal antibody. Cell culture for chlamydia currently is performed by only a few laboratories (primarily research centers) (3).

Although antigen detection methods for identification of *C. trachomatis* revolutionized the clinical availability of chlamydial diagnostics, their relative lack of sensitivity and specificity compared to tissue culture and especially nucleic acid amplification tests has limited their clinical usefulness (43,44) (see Chapter 5 for detailed description). Development of specific DNA probes for *C. trachomatis* (PACE 2) has led to their

being the most commonly used diagnostic test for *C. trachomatis*, especially for screening purposes. Compared to culture, antigen detection, and PCR, the sensitivity and specificity of the PACE 2 probe is in the range of good EIAs but less than that of nucleic acid amplification tests (45,46 and 47). Numerous investigations using PCR for chlamydial infections have been reported. Table 2.9 summarizes several studies of the sensitivity of chlamydia culture, PCR, and EIA for endocervical specimens.

At the University of Pittsburgh/Magee-Womens Hospital, we have performed studies where the enhanced sensitivity of PCR analysis was exploited by the collection of vaginal introitus specimens (48,49). Reasoning that minute amounts of DNA from urethral and cervical infections might deposit adequate amounts of chlamydial DNA in the vagina for application and detection by PCR, vaginal swabs were obtained from patients, along with culture specimens from the urethra and cervix (48). Eleven women were found to be positive for chlamydia infection by culture, whereas 10 of these 11 women were positive by PCR for chlamydial DNA obtained from vaginal swabs. Of the 11 women found to be culture positive from the cervix, eight were culture positive from the urethra. This preliminary work represents an alternative procedure that may offer the patient the opportunity to collect her own vaginal specimen for subsequent drop-off or mailing of the specimen to a centralized STD-PCR laboratory. This self-collected chlamydia specimen may eliminate the need for pelvic examinations in certain clinical situations, enhance the screening of adolescents for chlamydia, and permit greater access to patients who are discouraged from seeking chlamydia testing due to limited laboratory, physician, or health care facilities. In fact, we recently demonstrated the effectiveness of this approach among young female adolescents.

A major limitation to widespread screening of asymptomatic males for chlamydial genital infection has been the need to obtain urethral specimens using a swab (50). Screening urine samples with a leukocyte esterase (LE) dipstick has been demonstrated to be a useful tool to identify men with urethritis attributable to *C. trachomatis* or *N. gonorrhoeae* (51). However, this approach has a relatively low specificity (false-positives) and does not identify the causal agent (50). Subsequent studies demonstrated that testing urine specimens by EIA to detect chlamydial antigen was a sensitive and specific screening test for asymptomatic male carriers of *C. trachomatis* (52,53). Gene et al. (50) reported that EIA screening of LE-positive urine specimens was a cost-effective strategy for detecting asymptomatic chlamydial infections in males. These authors noted that positive EIA results in low-risk populations need to be confirmed. Shafer et al. (54) demonstrated that the optimum clinical and cost-effective approach was a combination of nonspecific screening of first-void urine for polymorphonuclear leukocytes or LE, followed by specific testing with EIA with DFA confirmation.

Unfortunately, this approach has not been demonstrated to be effective for screening asymptomatic females for chlamydial infection. Thus, to date, screening of asymptomatic females for chlamydial infection has required a pelvic examination with a speculum examination to obtain specimens from the endocervical canal. As described earlier, we demonstrated that a vaginal swab PCR-based test for *C. trachomatis* could be a useful, noninvasive screening test for asymptomatic chlamydial genital infection in women (48,49). Both PCR and LCR technology have been applied to urine-based screening to detect *C. trachomatis* among asymptomatic females as well as males. Preliminary results in genitourinary infections have been

very encouraging (27,28,29,30,31 and 32). The third pathogen capable of producing cervicitis is HSV. Unlike *N. gonorrhoeae* or *C. trachomatis,* HSV involves the ectocervix as well as the endocervix. To date, identification of HSV is routinely accomplished with culture isolation of the viral agent in cell culture. The urogenital swab of the newest lesion is placed in a viral transport media such as Hanks or Earle balanced salt solution supplemented with broad-spectrum antimicrobial agents that will inhibit and kill contaminating bacteria and fungi. For best results, these viral specimens should be delivered to the microbiology laboratory immediately after collection. Anticipated delays of more than 24 hours between collection and culture require viral specimens to be frozen at 70°C to 80°C. Refrigeration of viral specimens held for less than 24 hours is recommended for samples awaiting inoculation into cell culture. Cytopathic effect is observed in most HSV cultures in 18 to 24 hours; 99% of positive cultures are identified within 96 hours. Cytologic examination of specimens demonstrating multinucleated giant cells using Wright-Giemsa or fluorescent antibody stains from the cervix is diagnostic of HIV infection, but negative smears do not rule out HSV infection. Immunoperoxidase staining of HSV is helpful if the result is positive, but a negative result may not rule out the presence of low copy numbers of HSV particles.

Vaginitis is the most common infectious disease seen by obstetrician-gynecologists. The agent responsible for the signs and/or symptoms of vaginitis can be identified rapidly in the office or clinic using simple and inexpensive methodology. The diagnosis of trichomoniasis is generally made by demonstration of motile *T. vaginalis* organisms on a wet mount preparation; culture of the organism in Diamond TYM medium or Trichicult over a 7-day period is the most sensitive procedure. Direct fluorescent antibody staining can be conducted.

Candida albicans infection usually is identified by the presence of pseudohyphae on a 10% KOH preparation or methylene blue stain. Although culture is available, it is generally unnecessary; Nickerson or Sabouraud media are very sensitive and are commonly used by microbiology laboratories.

Diagnosis of bacterial vaginosis does not require culture methodology. Nearly 60% of normal healthy women have *Gardnerella vaginalis* as part of their normal vaginal flora. Clinical criteria for diagnosis of bacterial vaginosis include demonstration of (a) a homogeneous vaginal discharge; (b) vaginal pH more than 4.5; (c) presence of “clue” cells (squamous epithelial cells to whose border are adhered *G. vaginalis*); and (d) release of a “fishy” amine odor on addition of 10% KOH to vaginal secretions (55). Spiegal (56) and Nugent et al. (57) described the use of a vaginal Gram stain for diagnosis of bacterial vaginosis. They suggest that a normal Gram stain contains lactobacilli, whereas patients with bacterial vaginosis have large numbers of a variety of other organisms.

Infections Of The Upper Genital Tract

Infections involving the upper genital tract (i.e., uterus, fallopian tubes, ovaries, and pelvic peritoneal cavity) are typically of mixed anaerobic-aerobic bacterial etiology (58) and are discussed in depth in Chapter 8. Pelvic inflammatory disease (PID) is associated with sexually transmitted organisms such as *N. gonorrhoeae* and*C. trachomatis* (59). Table 2.10 lists the more common type of soft tissue pelvic infections encountered in clinical practice, the appropriate site from which to obtain specimen(s), and the microorganisms assumed to be pathogens at these anatomic

sites. The specific microorganisms involved in these pelvic infections are discussed in Chapter 1.

Type of Infection	Appropriate Site for Specimen	Microorganisms Cultured
Endomyometritis	Endometrial aspirate	Anaerobic bacteria Facultative bacteria ? Chlamydia trachomatis
Pelvic inflammatory disease	Endocervix	Neisseria gonorrhoeae C. trachomatis
	Fallopian tube by laparoscopy	N. gonorrhoeae C. trachomatis
	Culdocentesis	Anaerobic bacteria
	Endometrial aspirate	Facultative bacteria
Posthysterectomy pelvic cellulitis	Peritoneal cavity fluid (culdocentesis)	Anaerobic bacteria Facultative bacteria
Pelvic abscess	Aspirate of abscess contents or ideally a piece of tissue from the abscess wall	Anaerobic bacteria Facultative bacteria

TABLE 2.10. APPROPRIATE MICROBIOLOGIC SPECIMENS FROM SOFT TISSUE INFECTIONS OF THE FEMALE UPPER GENITAL TRACT

The pathogens involved in upper genital tract infections generally arise from the normal flora of the vagina and cervix (except *N. gonorrhoeae*, *C. trachomatis,* and group A b-hemolytic streptococcus); therefore, microbiologic isolation attempts must bypass the heavy bacterial colonization of the lower female genital tract (58). In addition, anaerobic bacteria are such prevalent pathogens in pelvic infections that microbiologic procedures should be used that are adequate and appropriate for the recovery and identification of anaerobic bacteria.

In patients with endomyometritis following delivery (vaginal or cesarean) or abortion, the appropriate specimen for culture is an endometrial isolate. This specimen can be best obtained using a telescoping double plastic cannula with an inner wire brush (60), which nicely prevents contamination with the vaginal and cervical flora, or the Pipelle device (Unimar, Wilton, CT), which also has been demonstrated to provide excellent endometrial specimens for microbiologic analysis (61). The cervix is not an appropriate site from which to obtain specimens for anaerobic and facultative bacteria, because the cervix has a rich microflora of both anaerobes and aerobes and does not accurately reflect the pathogens present in the upper genital tract. Patients with acute PID should have their cervix cultured, sampled for antigen, or assayed by nucleic acid amplification tests for both *N. gonorrhoeae* and *C. trachomatis* as described in the section on Infections of the Lower Female Genital Tract. Specimens from the endometrial aspirate are submitted for isolation of anaerobic and facultative bacteria, *C. trachomatis,* and *N. gonorrhoeae.* Nucleic acid amplification technology can be used to detect *C. trachomatis* from endometrial specimens. *In situ* hybridization also has been used on endometrial biopsy specimens (62).

The fallopian tube is the ideal site to obtain microbial specimens from patients with acute PID. Laparoscopy is required to obtain specimens and cultures from the tube but unfortunately is limited due to logistic and economic concerns. When laparoscopy is performed, cultures should be obtained from the fallopian tubes and

cul-de-sac for anaerobic and facultative bacteria, *N. gonorrhoeae* and *C. trachomatis.* The usefulness of direct smears of fallopian tube specimens with fluorescein-labeled monoclonal antibody against *C. trachomatis* was described by Kiviat and coworkers (62). Culdocentesis was widely used to obtain peritoneal fluid as a specimen, which is processed for anaerobic and facultative bacteria, *N. gonorrhoeae,* and *C. trachomatis.* Culdocentesis is superior to cervical cultures but is of limited value because of the high degree of vaginal contamination of these specimens (63). Endometrial aspirates have been used for the culture of anaerobic and facultative bacteria, *N. gonorrhoeae,* and *C. trachomatis* from the upper genital tract of patients with acute PID (64). The endometrial aspirate is a more accurate reflection of the microbiologic etiology of PID than is culdocentesis and is better tolerated by patients (59). Specimens from patients with posthysterectomy pelvic cellulitis should be obtained from the peritoneal cavity. This is best accomplished via culdocentesis and submitted for anaerobic and facultative cultures. In the presence of postoperative cuff abscess, the aspirate of the abscess is the ideal specimen and should be cultured for anaerobic and aerobic bacteria. Similarly, the appropriate specimen from patients with a pelvic abscess is purulent material aspirated from the abscess (obtained in the operating room or percutaneously) and evaluated for anaerobic and facultative bacteria and, in the case of tuboovarian abscess, *N. gonorrhoeae*. The ideal specimen from an abscess for culture, DNA amplification, or *in situ* hybridization is material or tissue obtained from the abscess wall at the time of surgery.

Collection, handling, and transport of specimens obtained from the upper genital tract require special procedures, because anaerobic bacteria must be obtained using methods that ensure their survival. Aspiration of fluid or pus into a syringe is the preferred method for collection of these specimens. The syringe should not be used for transport; rather, the specimen should be injected into an anaerobic transport vial. Swabs are not recommended to obtain specimens for anaerobic cultures if fluid is available. Use of transport media is easy and convenient, but is associated with a false-negative rate of 40%. The preferred method is to use anaerobically sterilized, prereduced cultures, such as CO_2-filled tubes or gas packs. Rubber-stoppered collection tubes that had O_2 evacuated with CO_2 are reliable tools for collection of aspirates (65). Anaerobic vials are commercially available; these include Port-A-Cul (BBL Microbiology System, Cockeysville, MD), Anaerobic Transport Medium (Anaerobe Systems, San Jose, CA), and Anaport and Anatube (Scott Laboratories, Fiskeyville, RI). A single specimen will suffice for anaerobic and facultative organisms; the latter grow under anaerobic as well as aerobic conditions. All anaerobic specimens require prompt transport to the infectious disease laboratory if they are to survive.

The Gram stain is an important clinical tool in the management of upper genital tract infections. Gram staining allows for prompt identification of bacterial pathogens and provides a quality control mechanism on the culture techniques being used, especially as related to the recovery of anaerobes. The presence of bacteria on the Gram-stained smear in the face of negative culture results should raise concerns as to the adequacy of the anaerobic procedures being used for the collection, handling, or transport of specimens to the laboratory and/or the laboratory's capability to grow and identify anaerobic bacteria.

Urinary Tract Infections

Infections involving the urinary tract are among the most common infections seen by obstetrician-gynecologists in their practice. Thus, it is important to understand the methods available for proper collection and handling of urine specimens for microbiologic evaluation (1). Although the absolute criteria for diagnosis of UTI in both symptomatic and asymptomatic patients rest on the presence of a positive culture from a properly collected and handled urine specimen that has not been contaminated by vulvar/vaginal bacteria, immediate microscopic examination of urine sediment often may be helpful (1). Identification of bacteria in urine allows for initiation of empiric therapy in the symptomatic patient while waiting for culture confirmation of UTI.

A midstream clean-catch urine is the most widely obtained specimen for both culture and microscopic evaluation of urine. It is important that the patient be properly instructed on how to obtain a midstream, clean-catch urine specimen. A minimum of 4 hours should have elapsed since the last voiding. An alternative method, favored by some urologists but not commonly used by obstetrician-gynecologists, is suprapubic bladder aspiration. If this method is used, the specimen should be identified as such so that all growth is reported and identified (3).

Kass (66) popularized the use of quantitative urine cultures where the criterion of $^{3}10^{5}$ bacteria per milliliter became the diagnosis of UTI. This standard is reliable for acute pyelonephritis and asymptomatic bacteriuria. However, Stamm and coworkers (67) demonstrated that a criterion of $^{3}10^{5}$ bacteria per milliliter is unreliable in association with acute bacterial cystitis. These investigators noted a 50% false-negative rate with a single specimen using this criterion. In patients with acute cystitis, a midstream clean-catch urine with $^{3}10^{2}$ bacteria per milliliter is sufficient to confirm the diagnosis of cystitis (67).

Urine at room temperature is an excellent culture medium for bacteria. In such conditions, the number of bacteria in urine doubles every 45 minutes. Thus, a 6-hour delay at room temperature will result in 10^{3} bacteria per milliliter increasing to $^{3}10^{5}$ bacteria per milliliter. It is imperative that urine specimens be transported promptly to the laboratory. Refrigerate urine specimens if a delay of more than 1 to 2 hours will occur.

The most rapid method to detect $^{3}10^{5}$ bacteria per milliliter is microscopic examination of a urine specimen. A Gram stain of a well-mixed, unspun urine demonstrating 2 bacteria per high-power field has 90% correlation with results of quantitative bacteriologic cultures. In addition, this procedure allows for determination of the adequacy of the specimen by demonstrating the absence of epithelial cells. In contradistinction, demonstration of pyuria (more than five white blood cells per high-power field of a centrifuged urine specimen) has variable sensitivity (pyuria is present in 90% of symptomatic UTIs, but in only 50% of asymptomatic bacteriuria) and poor specificity (3,68).

Several chemical methods have been developed to detect significant bacteriuria in urine specimens (3). These include the Griess test, tetrazolium reduction, glucose oxidase, and catalase. The best of the chemical tests is the Griess test, which measures nitrite. However, it is valid only for Gram-negative bacteria, is useful only if the result is positive, and has a false-negative rate of nearly 50%. It is commercially

available as N-Multistix (Ames), Microstix-3 (Ames), Chemstrip 8 (Bio Dynamics), or Bac-U-Dip (Warner/Chilcott).

In office practice, especially for routine screening of prenatal patients, a multitude of office urine culture kits are available. Basically, there are three categories of culture kits: (i) dip strip with culture pads (Microstix-3); (ii) coated shell, coated tube, or agar cup (Testuria, Speri-Test, Bacturcult); and (iii) dip slide (Uricult; Medical Technology Corp.) and Dipchex (York Scientific). Of these, the dip slide is the most versatile and easiest to use. Most importantly, it is the most accurate, with a 99% correlation with standardized quantitative culture techniques. Thus, it permits inexpensive culture both before therapy and as a test of cure. Any organism isolated remains viable for several weeks and is available to be sent to the laboratory for identification and susceptibility testing, if necessary.

Bacteremia

It is estimated that 200,000 cases of septicemia occur each year in the United States, with a 20% to 50% mortality rate (69,70). Fortunately, bacteremia is not a common occurrence in patients with infection on obstetric and gynecologic services (71). However, bacteremia represents a serious and potentially life-threatening complication of pelvic infections. Thus, it is important to recognize the presence of bacteremia. To optimize the ability to diagnose bacteremia, clinicians must recognize the clinical determinants of positive blood cultures.

Most bacteremias are intermittent and usually precede the onset of fever and chills. An exception is intravascular sources, such as endocarditis, in which bacteremias may be continuous (72). The sensitivity of most media used in blood culture attempts is two to three organisms per milliliter; however, the magnitude for bacteremia is low. Adults with endocarditis or Gram-negative bacteremia generally have ten to 100 colony-forming units per milliliter (73,74). Previous antibiotic therapy (even up to 2 weeks before) may completely or partially suppress growth of bacteria, giving false-negative results.

The two major variables in detection of bacteremia are the timing of blood cultures and the volume of blood collected. In endocarditis, where bacteremia is continuous, two cultures (from separate venipunctures) at one time usually are adequate. Soft tissue pelvic infections are associated with intermittent bacteremias. In such bacteremias, Washington (74) demonstrated that the sensitivity of a single culture is 80%. Two separate cultures drawn at least 1 hour apart have 89% sensitivity, and three separate cultures drawn at least 1 hour apart have 99% sensitivity. The volume of blood is probably the single most important determinant of the appropriateness of a blood culture specimen (3,75). A 30-mL sample is associated with a 50% increase in positive results compared with a 10-mL sample, as is drawn by most laboratories. The current recommendation for adult patients is to draw at least two separate blood cultures totaling 30 to 40 mL (3). The optimal time for collection of blood specimens is just before onset of a chill (76); however, such an event cannot be anticipated.

It is crucial to differentiate the presence of true pathogens from contaminants when interpreting blood culture results (77). With pathogenic organisms, numerous cultures are positive, and less than 3 days are required for detection of organisms. Pathogenic organisms include Gram-negative bacilli, *S. aureus*, *Enterococcus faecalis*, viridans streptococci, anaerobes, fungi, and yeasts. *Staphylococcus*

epidermidis has become a recognized and serious pathogen in certain clinical situations. This is especially true of nosocomial (hospital-acquired) infections in patients with central lines and invasive monitoring. In contrast, contaminants are characterized by a single positive culture, and more than 3 days are required for detection of organisms. Typical contaminants in blood cultures include *Corynebacterium* sp, *Propionibacterium* sp, and, in most circumstances, especially community-acquired infections, *S. epidermidis.* To prevent such contamination, the venipuncture site must be carefully disinfected before obtaining the blood culture. This is crucial because these commensals may be involved in infections of implanted prosthetic material. To help identify true catheter-related infections, semiquantitative catheter tip cultures per the guidelines of Maki et al. (78) are used. A significant advance has been the introduction of continuous-monitoring blood culture systems (3,77). With these systems, a growth reading is performed automatically every 10 to 20 minutes, which allows detection of positive cultures as quickly as possible. In addition, the bottles need not be opened to detect growth, which significantly reduces the risk of contamination (3).

Although the incidence of bacteremia arising from soft tissue pelvic infections is relatively low, blood cultures are a valuable diagnostic tool in evaluating such infections. A positive culture demonstrating bacteremia identifies a subgroup of patients with severe pelvic infections and who may require more lengthy courses of therapy.

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3

GROUP B STREPTOCOCCI

Since the last edition of this text, considerable progress has been made in the prevention of perinatal group B streptococcal (GBS) infections. In the spring of 1996, the Centers for Disease Control and Prevention (CDC) published recommendations for two preventative strategies. The American College of Obstetricians and Gynecologists (ACOG) endorsed these recommendations. In the ensuing years, there was growing evidence that adoption of these guidelines reduced the likelihood of GBS perinatal infection. However, we do not have a panacea, as both immediate and long-term questions remain. This heavily revised chapter will detail the national guidelines as well as provide insight into their limitations.

In 1933, Lancefield (1) used serologic techniques to subdivide b-hemolytic streptococci into specific groups, which she named A, B, D, and E. The various groups of streptococci, their taxonomic designations, and hemolytic reactions on blood agar are listed in Table 3.1. On blood agar, the b reaction is clear or there is complete hemolysis around the bacterial colony; the b reaction is a greenish discoloration or there is partial hemolysis around the colony; and the b reaction is an absence of hemolysis around the colony. Most microbiology laboratories report groups C and G “as b-hemolytic streptococci, not groups A, B, or D.”

Group	Common Species Designation	Reaction on Blood Agar
A	S. pyogenes	β, rarely α
B	S. agalactiae	Usually β, rarely α or γ
C	S. equi, S. zooepidemicus, S. equisimilis, S. dysgalactiae	Usually γ, except S. dysgalactiae is α
D, enterococcus	S. faecalis, S. faecium	Usually γ, occasionally α or β
D, not enterococcus	S. bovis, S. equinus	Usually γ, occasionally α or β
G	S. anginosus	Usually β
Viridans, not group D	Many species	α or γ
	S. pneumoniae	α

Adapted from Buchanan RE, Gibbon NE. Bergey's manual of determinative bacteriology. 8th ed. Baltimore: Williams & Wilkins, 1974.

TABLE 3.1. AEROBIC STREPTOCOCCI: TAXONOMIC CLASSIFICATION AND REACTION ON BLOOD AGAR

Although GBS were recognized in veterinary medicine for many years as a cause of bovine mastitis, they were virtually ignored as human pathogens until 1964, when Eickhoff and associates (2) noted the role of GBS in perinatal infections. In the following years, GBS became the leading bacterial pathogens in perinatal infections, replacing *Escherichia coli* as the most frequent microorganisms associated with bacteremia or meningitis among infants during the first 2 months of life (3). In 1990, it was estimated that there were 7,600 cases of neonatal GBS disease, accounting for an incidence rate of 1.8 per 1,000 liveborn infants. These cases resulted in an estimated 310 deaths from GBS disease among infants younger than 90 days of age in the United States (4,5).

Group B streptococcus has been recognized as one of the most important pathogens in obstetric patients as well. This organism causes urinary tract infections, amnionitis, postpartum endometritis, wound infection, and intrapartum and/or postpartum bacteremia (6,7). It may lead to premature rupture of membranes (PROM) and preterm delivery (4,5,8).

ORGANISM

Group B streptococcus *(Streptococcus agalactiae)* is a facultative Gram-positive diplococcus. Colonies of GBS on sheep blood agar produce a characteristic appearance with narrow zones of b hemolysis surrounding the colonies, which are gray-white, flat, and mucoid. Approximately 1% of GBS isolates are nonhemolytic or b-hemolytic. Definitive microbiologic identification of GBS requires serologic techniques for detection of the group B antigen. Group B streptococci can be subdivided further into serotypes based on antigenic carbohydrates as Ia, Ib, II, III, IV, and V. In the past, the distribution of serotypes of GBS has been similar for mother-neonate pairs. Approximately one third of isolates are type Ia or Ib; one third are type II; and one third are type III (3). More recently, serotypes IV and V have been identified. In addition, a former subtype Ic has been categorized as identical to subtype Ia. In recent surveys, distribution of GBS serotypes is as follows: type Ia, 27% to 36%; type Ib, 2.4% to 12.5%; type II, 9% to 12%; type III, 14% to 43%; and type V, 10% to 29%. Type IV isolates are seen very infrequently, and approximately

0% to 3% cannot be typed (9).

EPIDEMIOLOGY

Asymptomatic vaginal colonization with GBS occurs in approximately 20% (range 4.6% to 40.6%) of pregnant women (Table 3.2) (2,10,11,12 and 13). The gastrointestinal tract is the likely reservoir (4). The reported prevalence of vaginal colonization with GBS in gravid women varies according to geographic locale, age, gravidity, duration of gestation, and location and number of sites cultured. Obtaining specimens for culture from both the anorectum and the distal vagina increases the likelihood of obtaining GBS by a considerable percentage (5% to 25%) over vaginal culture alone (4). Within the genital tract, the highest isolation rates are reported from the introitus and the lowest from the cervix. Pregnancy does not influence colonization rates.

Feature	Rate
Maternal carriage	20% (range 10%–30%)
Early-onset neonatal GBS sepsis	1.5/1,000 live births (0.15%)
Neonatal colonization overall	5%–20%
Neonatal early-onset GBS sepsis if mother positive	Approximately 1%

GBS, group B streptococcus.

TABLE 3.2. EPIDEMIOLOGY OF GROUP B STREPTOCOCCUS PERINATAL INFECTION

The choice of culture medium is a crucial determinant of the prevalence of GBS. The highest yield of GBS occurs when a selective broth medium, such as Todd-Hewitt broth with sheep blood, nalidixic acid, and gentamicin, is used. When selective media are not used for cultures of the genital tract, up to 50% of colonized women will be missed (i.e., the sensitivity will be as low as 50%).

The presence of GBS in the maternal genital tract is the major determinant of both infection in the neonate and colonization of the newborn (10,12,14,15 and 16). Vertical transmission from mother to fetus occurs either via an ascending route *in utero,* most commonly with ruptured membrane (but occasionally with intact membranes), or by acquisition during passage through the birth canal intrapartum. The risk of transmission has been shown to range from 42% to 72% among neonates born to colonized mothers; approximately only 8% of infants born to noncolonized mothers become colonized (10,11,12 and 13). Based on these prospective studies, nearly two thirds of infants born to colonized mothers will be colonized with GBS. Despite high prevalence rates for vertical transmission, the incidence of GBS infection during the first 7 days of life ranges from 1.3 to 3 per

1,000 livebirths; after 7 days, the range is 1 to 1.7 per 1,000 livebirths (4,10). (These data are from an era before use of prophylaxis.) Only 1% to 2% of infants of colonized women develop early-onset GBS infection.

In addition to maternal-infant transmission, nosocomial acquisition of GBS occurs (17). From 16% to 47% of nursery personnel are carriers of GBS and may be sources for neonatal transmission (3). Studies have demonstrated nosocomial transmission rates of GBS in neonates born to culture-negative mothers. In addition, cross-contamination of infants may arise via nursery personnel (3). Nosocomial transmission rates of GBS in neonates born to culture-negative mothers range from 13% to 43% (17). Whether late-onset GBS infection is largely due to nosocomial acquisition of GBS is unclear. Both nonmaternal and maternal sources have been implicated (3).

Risk factors that predispose the neonate to clinical infection have been identified (Table 3.3).

- Prematurity (<37 weeks' gestation)
- Clinical chorioamnionitis, intraamniotic infection, maternal fever in labor (often defined as >100.4°F)
- Rupture of membranes for longer than 12–18 hr
- Previously delivered infant with invasive GBS disease
- GBS bacteriuria in this pregnancy

[a]In some studies, heavy maternal colonization, low maternal serum type-specific antibody levels, and Black race also have been risk factors.
GBS, group B streptococcus.

TABLE 3.3. RISK FACTORS FOR EARLY-ONSET NEONATAL INFECTION WITH GROUP B STREPTOCOCCI[a]

Investigations have shown consistently that there is a significant 10- to 15-fold increase in the risk for GBS early-onset infection in preterm infants (10,14,15 and 16,18). Baker and Barrett (10) reported that 80% of infants with GBS disease weighed less than 2,500 g. Boyer and coworkers reported that as birthweight decreased, attack rates for GBS increased (Table 3.4) (14).

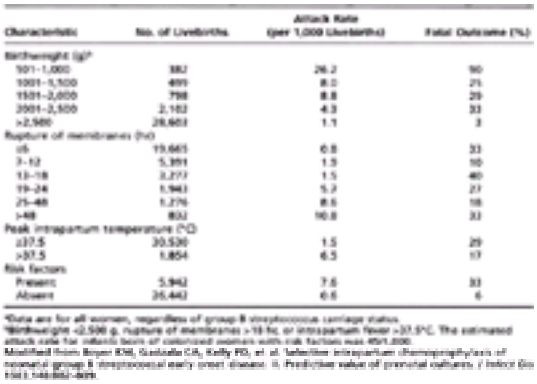

TABLE 3.4. ATTACK RATES OF NEONATAL GROUP B STREPTOCOCCAL EARLY-ONSET DISEASE ACCORDING TO PERINATAL CHARACTERISTICS[a]

Numerous studies found duration of rupture of the membranes (ROM) to be an important correlate of neonatal GBS infection (15). Boyer and colleagues (15) noted that as the duration of ROM increased, attack rates for GBS infection also increased, from 0.8 per 1,000 infants with ROM of 6 hours or less to 10.8 per 1,000 in those with durations greater than 48 hours. In this study, the relative risk of developing GBS early-onset disease for infants with ROM for more than 48 hours was 7.2-fold higher than that for infants with ROM for less than 18 hours (Table 3.4) (15). Further, Boyer and colleagues estimated that, in their population, the attack rate of GBS sepsis was 45 per 1,000 infants born to colonized women with perinatal risk factors (birthweight less than 2,500 g, ROM more than 18 hours, or intrapartum fever) (15). The relationship of GBS to premature birth and PROM is discussed in Chapter 17.

Intrapartum fever, clinical chorioamnionitis, and clinical intraamniotic infection are perinatal risk factors associated with increased risk for early-onset GBS sepsis (Table 3.3 and Table 3.4) (10,15). Boyer and coworkers (15) noted that attack rates for GBS were 6.5 per 1,000 infants among mothers with intrapartum fever versus 1.5 per 1,000 infants of afebrile mothers.

Neonates delivered through birth canals heavily colonized with GBS are significantly more likely to acquire GBS than those born to mothers with small numbers of GBS in their vaginas (11).

Additional risk factors have been suggested. Baker and Kasper (19) proposed that the offspring of mothers who lack antibodies to GBS type III have a greater risk of acquiring type-specific disease. Baker and Edwards (3) suggested two mechanisms that result in low levels of neonatal antibody to GBS: it either reflects low maternal levels and lack of acquired immunity in the mother, or failure of adequate concentrations of these immunoglobulin G (IgG) antibodies to be transported transplacentally to the fetus. The very small preterm infant (younger than 30 weeks) may be significantly compromised by the second mechanism, because nearly two thirds of maternally derived IgG is actively transported from mother to fetus in the last 10 weeks of pregnancy.

In a CDC review of 278 cases of infant disease, there were 247 (80.7%) early-onset cases and 59 (19.3%) late-onset cases. The case fatality rate was 5.8% (16/278), with no difference in rates for early and late-onset disease (5.7% and 6.0%, respectively). Thirteen (81.3%) of the deaths occurred in infants of less than 34 weeks' gestation, and eight of the infants were black (20). In a population-based study, 71 cases of early-onset disease and 37 cases of late-onset disease were compared with 65,000 births in the same period (1982 to 1983). Infants with early-onset disease were more likely to be black (relative risk [RR] 2.4, confidence interval [CI] 1.4–3.9), of low birth weight (RR 2.03, CI 1.04–4.0), and born of teenage mothers (RR 2.2, CI 1.3–3.7). [Relative risk values shown are from a multivariate analysis for all pregnancies (21).]

Combined data from earlier (1964 to 1983) series indicated that the greatest threat of GBS infection was to the premature infant. The likelihood of an infected premature baby surviving was 34% (38/110), whereas the likelihood of survival for term infants was 83% (65/78). Later series revealed improved survival rates among both preterm and term infants with GBS sepsis. In two large series from 1992, overall survival was reported at 86% and 94%, but was still lower (72%) among preterm infants (20,22).

Because bacteremia is present at birth in a large proportion of neonates with early-onset GBS disease, most cases (67% to 88%) of GBS early-onset disease have an intrauterine pathogenesis (15,23).

The epidemiology and pathogenesis of late-onset GBS infection (occurring more than 7 days after birth) are not as clear as for early-onset disease (3). Serotype III strains account for most late-onset GBS infection. The GBS organisms responsible for late-onset disease are acquired either by maternal-neonatal vertical transmission or from nosocomial sources. In a CDC survey of 306 cases of GBS sepsis among infants younger than 90 days of age, only 19% were late in onset, and case fatality rates were similar for early- and late-onset disease (5.7% and 6.0%, respectively) (20).

CLINICAL MANIFESTATIONS

Neonatal Infection With Group B Streptococcus

Two clinically distinct neonatal GBS infections have been identified. *Early-onset GBS disease* appears within the first week of life, usually within the initial 48 hours. In 60% of infants, early-onset GBS sepsis presents within 24 hours of birth. Early-onset GBS infection often is characterized by rapid clinical deterioration. It occurs most often in infants born to mothers with risk factors for GBS neonatal infection.

The three major presentations of early-onset GBS infection are septicemia (bacteremia and clinical signs of sepsis), pneumonia, and meningitis. Respiratory symptoms and signs, such as grunting, tachypnea, apnea, and/or cyanosis, usually are the earliest clinical findings (3). Hypotension occurs in 25%. Additional symptoms and signs similar to those associated with any bacterial infection (lethargy, poor feeding, hypothermia or fever, pallor, and jaundice) are present. Meningitis is present in approximately 30% of early-onset GBS infections. Pneumonia is present in 40% of infants with early-onset GBS infection, and almost all of these infants present with

grunting, tachypnea, and apnea.

Late-onset GBS disease occurs more insidiously. It usually occurs after the first week of life and up until 12 weeks of age. Most of these infants (85%) have meningitis as the prominent clinical manifestation. The presenting symptoms in newborns with meningitis include fever (nearly 100%), irritability and/or lethargy, and poor feeding. Antecedent upper respiratory tract symptoms were present in 20% to 30% of meningitis cases. Late-onset disease may result in localized infections involving the middle ears, sinuses, conjunctiva, breasts, lungs, bones, joints, and skin.

Meningitis is related to the serotype of GBS. More than 80% of early-onset GBS infections with meningitis present are due to type II organisms. More than 90% of late-onset disease (in which meningitis usually is present) are due to type III GBS. These findings are in contrast to the distribution of GBS serotypes among asymptomatic maternal carriers, where one third have type Ia, Ib, or Ic organisms; one third have type II; and one third have type III.

Whereas early-onset disease has been associated with transmission from the mother's genital tract either before labor or during parturition, such a route of transmission is thought to occur less frequently in late-onset disease. Nosocomial transmission of GBS can occur in the nursery from colonized nursing staff or by cross-colonization from other infants.

Maternal Infection With Group B Streptococci

Group B streptococcus now is recognized as an important cause of maternal infections as well as of neonatal sepsis. Among cases of GBS puerperal infection, bacteremia occurred in 31% to 35% (usual rate in obstetrics is 10%). Characteristically, women with GBS puerperal infection develop high spiking fever within 12 hours of delivery. Other clinical features include tachycardia, chills, and tender uterine fundus and parametrium. However, at the time of the first fever spike, few localizing signs or symptoms may be present (see Chapter 20).

Group B streptococci also cause maternal urinary tract infection (both bacteriuria and symptomatic disease), amnionitis, and wound infection (see Chapter 18 and Chapter 21).

DIAGNOSIS OF GROUP B STREPTOCOCCAL INFECTION

The “gold standard” for diagnosing maternal genitourinary colonization with GBS is the culture, when it is performed using selective medium. The optimal medium for cultivating GBS is a selective broth medium, such as Lim or selective broth medium (SBM) broth, which contains gentamicin and nalidixic acid. These antibiotics inhibit the growth of Gram-negative Enterobacteriaceae and other bacteria in the normal genital tract flora that could interfere with the recovery and identification of GBS.

Because the great majority of colonized neonates (~9%) are asymptomatic, detection of colonization requires culture identification of GBS. None of the clinical manifestations of neonatal disease is sufficient to confirm GBS disease in the absence of a positive culture of the blood or cerebrospinal fluid. A presumptive or

“clinical” diagnosis sometimes is made when there is a suggestive clinical picture accompanied by positive cultures from peripheral sites such as the umbilicus, oropharynx, and rectum.

Within the past few years, there has been great interest in tests for rapid identification of GBS from the maternal genital tract. These tests include Gram stain, immunofluorescent antibody test, colorimetric assay using starch serum media, and antigen detection by a variety of methods, such as coagglutination, latex agglutination, enzyme immunoassay, and DNA probes. These tests were reviewed in an excellent work by Yancey and colleagues (24) (Table 3.5) The Gram stain has many limitations, mainly low sensitivity and poor positive predictive value (25).

Test	Sensitivity	Positive Predictive Value
Gram stain	34%–100%	13%–33%
Immunofluorescent	33%–49% (6 hr)	89%
antibody	81% (12 hr)	
Starch serum medium		
Nurse performed	45% (12 hr)	65%
Technician performed	93% (12 hr)	96%
Antigen detection methods		
Coagglutination	4%–88%	
Latex agglutination	15%–88%	15%–92%
Enzyme immunoassay	11%–74%	24%–100%
Nucleic acid probe	68%–100%	

Adapted from Yancey MK, Armer T, Clark P, et al. Assessment of rapid identification tests for genital carriage of group B streptococci. *Obstet Gynecol* 1992;80:1038–1047.

TABLE 3.5. RAPID IDENTIFICATION TESTS FOR GROUP B STREPTOCOCCUS

Methods using starch serum media have better sensitivity and predictive values (in the 90% range when performed by laboratory technicians), but the requirement for an incubation period of 12 hours and difficulties in interpretation by labor and delivery staff make this approach impractical (24).

Numerous reports have assessed the rapid antigen detection tests. Overall, the sensitivity of these tests for detection of all colonized women varies from as low as 4% to as high as 88%. In 17 studies evaluated, the sensitivity was 60% or less in 13 studies. Positive predictive values varied from 15% to 100%. These tests perform better with heavy colonization, and the inability of current methods to detect women with light colonization is a serious drawback.

A promising rapid technique currently available is the DNA probe. Results from a preliminary report have been encouraging, with sensitivity of 71%, specificity of 90%, positive predictive value of 61%, and negative predictive value (NPV) of 94% after an incubation of 3.5 hours (26). No currently available rapid diagnostic test has sufficient sensitivity and positive predictive value to be cost effective and to replace the culture using selective media as the screening technique of choice (27).

TREATMENT OF GROUP B STREPTOCOCCAL INFECTION

Penicillin remains the drug of choice for symptomatic GBS infection in mothers or neonates. However, in most instances, treatment must begin empirically before culture results are available. Maternal infections such as amnionitis or postpartum endomyometritis usually are polymicrobic; thus, treatment requires a broad-spectrum approach, as discussed in Chapter 6. In these instances, a broader-spectrum approach for empirically treating the mother is required. Ampicillin is a frequently used and very effective agent in such situations and provides adequate treatment for GBS. The new semisynthetic penicillins (piperacillin, mezlocillin, ticarcillin) and first- and second-generation cephalosporins have very good *in vitro* activity. Erythromycin and clindamycin have been thought to provide very good coverage, but resistance is now a concern, as will be discussed later. Although GBS are resistant to aminoglycosides, addition of gentamicin or tobramycin to one of the penicillins results in a synergistic action against GBS. Because ampicillin is capable of crossing into the cerebrospinal fluid, the most common pediatric recommendation for GBS neonatal infection is an ampicillin-aminoglycoside combination. Among the multitude of new third-generation cephalosporins, cefotaxime has activity against GBS comparable to that of penicillin G. Cefoperazone and ceftazidime have somewhat less activity.

PREVENTION OF GROUP B STREPTOCOCCAL INFECTION

As a result of the severity of GBS neonatal infection and the recognition that the major method of pathogenesis is vertical transmission, major efforts have addressed prophylactic strategies. The various approaches are listed in Table 3.6.

1. Antepartum antibiotics
2. Intrapartum antibiotics
3. Neonatal antibiotics
4. Maternal vaccination

TABLE 3.6. STRATEGIES FOR PREVENTION OF GROUP B STREPTOCOCCUS INFECTION

Antepartum Antibiotics

Attempts at reducing maternal carrier rates by antepartum prophylaxis generally have been unsuccessful (28). Hall and associates (28) noted that administration of ampicillin to gravid women with cervical colonization of GBS resulted in a significantly decreased colonization rate within 3 weeks of therapy, but the women

treated often were recolonized by the time of parturition. Infants of the treated mothers were colonized at the same rate as the control infants.

To circumvent the problem of a high percentage of reacquisition of GBS after attempted prophylaxis in the early third trimester, Merenstein and coworkers (29) evaluated the efficacy of an oral penicillin regimen at 38 weeks' gestation. They noted a significant reduction in maternal and infant colonization with GBS in the treatment group (mothers and sexual partners treated). However, this approach misses the group at greatest risk, the preterm pregnancies, in which neonatal mortality with GBS infection is much greater.

The attempt at antepartum prophylaxis against GBS is hindered by several factors. Mainly, it is difficult to eradicate GBS from the rectum because of the b-lactamase enzymes (which inactivate penicillin and ampicillin) produced by the Enterobacteriaceae in this locale. Accordingly, using antepartum antibiotics in pregnant women to prevent neonatal sepsis generally has been abandoned. Furthermore, use of oral antibiotics during prenatal care in women colonized with GBS (for the purpose of decreasing preterm birth) has not been shown to be effective (30). (Treatment of GBS bacteriuria, of course, is appropriate.)

Intrapartum Antibiotics

Use of intrapartum antibiotics has been established as an effective method to decrease neonatal colonization and early-onset disease (Table 3.7 and Table 3.8). Yow and colleagues (31) showed that use of intravenous ampicillin (500 mg/dose) during the intrapartum period in GBS-positive mothers prevented neonatal GBS colonization and disease. Boyer et al. (16) examined the effect of intrapartum ampicillin treatment on vertical transmission of GBS. Ampicillin virtually eliminated vertical transmission of GBS in the treatment group without perinatal risk factors and in the treatment groups with premature labor and/or prolonged ruptured membranes. Group B streptococcus colonization occurred in the neonates born to women who had intrapartum fever or less than 1 hour of ampicillin treatment before delivery. Combining a single antepartum screening culture for GBS with intrapartum intravenous ampicillin treatment at 26 to 28 weeks for mothers with suspected amnionitis, preterm labor, and/or PROM who are GBS carriers resulted in a significant reduction in the vertical transmission of GBS from mother to infant.

Study (Reference No.)	N	Method	Result (Sepsis per 1,000 Livebirths)
Garland et al. 1991 (35)	57,000	Nonrandomized trial, prophylaxis to all positives	Prophylaxis decreased rate from 1 to 0.5 (NS)
Katz et al. 1994 (36)	1,681/237	Descriptive, prophylaxis to all positives	0 (historic rate = 2, NS)
Gilbs et al. 1994 (33)	3,721/411	Descriptive, selective prophylaxis	1 (historic rate = 1.5, NS)

N, number screened/number of group B streptococcus carriers; NS, not significant.

TABLE 3.7. NONRANDOMIZED CLINICAL TRIALS OF INTRAPARTUM

PROPHYLAXIS AND NEONATAL OUTCOMES—SEPSIS

Study (Reference No.)	Treatment	Control	p Value
Motorras et al. 1991 (37)	0/60	3/65	0.245
Boyer and Gotoff 1986 (32)	0/85	4/79	0.052
Tuppurainen et al. 1989 (38)	1/88	5/111	0.252
Morales et al. 1986 (39)	0/37	3/30	0.09

Adapted in part from Ohlsson A, Myhr TL. Intrapartum chemoprophylaxis of perinatal group B streptococcal infections: a critical review of randomized controlled trials. *Am J Obstet Gynecol* 1994;170:910–917.

TABLE 3.8. RANDOMIZED CLINICAL TRIALS OF INTRAPARTUM PROPHYLAXIS AND NEONATAL OUTCOME—SEPSIS OR PNEUMONIA

In a subsequent study, Boyer and Gotoff (32) conducted a randomized, nonblinded, controlled trial of the effect of selective use of intrapartum ampicillin in women with these risk factors. Patients received either ampicillin 2 g intravenously initially, then 1 g intravenously every 4 hours until delivery or no ampicillin. For infants of mothers randomized to intrapartum ampicillin, therapy was continued with four doses of ampicillin (50 mg/kg/dose) intramuscularly every 12 hours until initial neonatal cultures were available. Infants of mothers randomized to no treatment were given antibiotics only if they became symptomatic. The ampicillin-treated group had significantly less neonatal colonization and significantly reduced neonatal bacteremia. In our experience at the University of Colorado, we found that using the latter strategy was complex (33).

Between 1986 and 1994, numerous other intrapartum approaches have been suggested and/or evaluated. In 1994, Rouse and colleagues (27) reviewed 19 different intrapartum strategies in a decision analysis. Of these, a strategy of universal prophylaxis, consisting of intrapartum administration of antibiotics to all women in labor, was believed to be a cost-effective strategy, based on decision analysis. In addition, a strategy of giving prophylaxis to all high-risk women in labor, following the recommendation of Minkoff and Mead (34) and of the ACOG (5), was believed to be a cost-effective strategy. Universal screening based on cultures at the end of the second trimester had considerable limitations, especially because of the modest predictive value of the 26-week culture for maternal culture status of women in labor. Strategies based on screening women in labor using a rapid test were judged to be not effective.

To avoid systemic side effects in the mother, Burman and coworkers (41) proposed and tested a novel technique. They reported a randomized, blinded trial of chlorhexidine douches given to women in labor to prevent neonatal GBS sepsis. Compared with placebo, chlorhexidine douches reduced the admission rate of

infants to the special care nursery from 5.4% to 2.8% for GBS-colonized mothers (*p* = NS) and from 2.9% to 2.0% overall (*p* = 0.04). However, this endpoint is soft, and there was no decrease in the culture-confirmed sepsis rate (2/1,000 in both groups) (41). Because many infants with GBS sepsis already are bacteremic at birth, vaginal douching may be too little prophylaxis, too late. In response to the need for national guidelines, the CDC developed prevention strategies through critical analysis of clinical trial data and a subsequent review by a multidisciplinary group of consultants. These guidelines were published in spring 1996 (4). Supporting documents then were issued by the ACOG (5) and the American Academy of Pediatrics (42). These guidelines recommended the following:

- Use of either a strategy based on late prenatal culture (at 35 to 37 weeks) as the primary risk determinant or a strategy based solely on clinical risk factors
- When the culture-based strategy is used, the offer of intrapartum antibiotic prophylaxis to all women who have a positive culture whether or not there are intrapartum risk factors
- Use of penicillin G as an alternative to ampicillin for intrapartum prophylaxis

In the approach based on screening cultures at 35 to 37 weeks, prophylaxis is recommended if any of the following conditions exists: a previously infected infant with invasive disease, GBS bacteriuria in this pregnancy, or delivery at less than 37 weeks. Patients are screened at 35 to 37 weeks, and all patients are offered intrapartum prophylaxis. A proviso of this strategy is that if a culture result is unknown, prophylaxis is given if the patient has a temperature greater than 38°C (100.4°F), the patient is in labor, or ROM duration is 18 hours or more. Special conditions required for the screening-based approach include the use of an optimal culture technique. This involves use of swabs from both the distal vagina and the rectum and use of selective broth media in the culture process. It is important to note that treatment of genital antenatal GBS colonization is not recommended, whereas treatment of GBS bacteriuria is recommended when diagnosed. Figure 3.1 shows an algorithm summarizing the approach based on prenatal screening cultures at 35 to 37 weeks. This algorithm is complex, and it is recommended that hospitals using this algorithm have copies of this figure readily available in the labor and delivery unit.

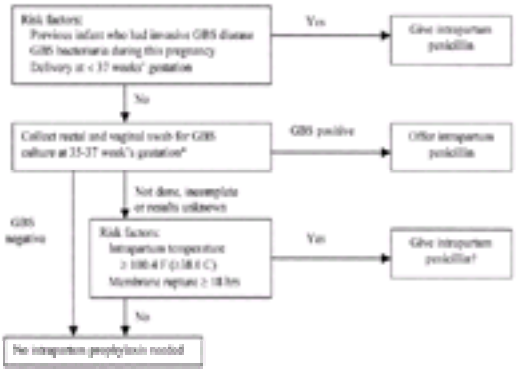

FIGURE 3.1. Prevention strategy using prenatal screening at 35 to 37 weeks' gestation.

Under the approach using risk factors, prophylaxis is given with one or more of the following risks:

- Previous infant with invasive GBS disease
- Group B streptococcus bacteriuria in this pregnancy
- Delivery at less than 37 weeks
- Duration of ROM 18 hours or more
- Temperature of 38°C (100.4°F)

The algorithm for this approach is shown in Fig. 3.2. Even though this approach is a simpler one, it is recommended that copies of this algorithm be available in hospitals using it so that compliance can be optimized. It is estimated that the approach based on screening at 35 to 37 weeks prevents a greater percentage of cases of early-onset neonatal sepsis due to GBS than does the approach based on risk factors. However, this estimate presumes there is excellent compliance with both approaches and that proper culture technique is followed with the screening-based approach. It is acknowledged that a larger percentage of gravid women will be exposed to intrapartum antibiotics with the screening-based approach. Another concern of the screening-based approach is that recognition of a positive culture at 35 to 37 weeks will lead to antibiotic treatment during the antepartum period in an attempt to eradicate the positive culture. Comparison of these two regimens is shown in Table 3.9. Box 1 shows the recommended regimens for intrapartum antimicrobial prophylaxis for perinatal GBS disease.

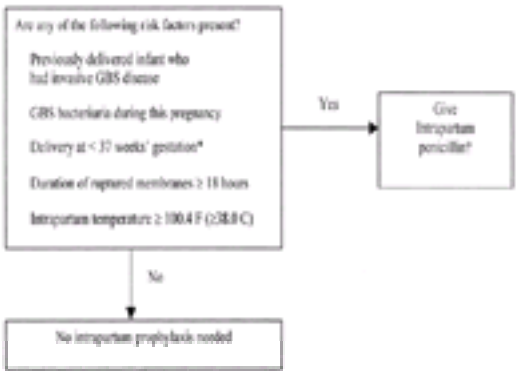

FIGURE 3.2. Prevention strategy using risk factors.

Feature	Screening at 35–37 Weeks	Risk Factors
Estimated gravid women given prophylaxis	27%	18%
Estimated cases of early-onset neonatal sepsis due to group B streptococcus prevented	86%	69%

Based on American College of Obstetricians and Gynecologists (ACOG). Prevention of early-onset group B streptococcal disease in newborns. ACOG Committee Opinion 173. Washington, DC: ACOG, 1996; and Rouse DJ, Goldenberg RL, Cliver SP, et al. Strategies for the prevention of early-onset neonatal group B streptococcal sepsis: a decision analysis. *Obstet Gynecol* 1994;83:483–494.

TABLE 3.9. COMPARISON OF TWO CENTERS FOR DISEASE CONTROL AND PREVENTION/AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGIST's strategies

Box 1

Recommended Regimens for Intrapartum Antimicrobial Prophylaxis for Perinatal Group B Streptococcal Disease

Recommended Penicillin G, 5 mU i.v. load, then 2.5 mU i.v. every 4 hr until delivery

Alternative Ampicillin, 2 g i.v. load, then 1 g i.v. every 4 hr until delivery

If penicillin-allergic:

Recommended Clindamycin, 900 mg i.v. every 8 hr

Alternative Erythromycin, 500 mg i.v. every 6 hr until delivery

These guidelines have been widely distributed and fairly widely adopted. A later section in this chapter discusses the aftermath of the 1996 guidelines, including areas of potential noncompliance, persisting clinical questions, and policy questions.

Note: If a patient is receiving treatment for amnionitis with an antimicrobial agent active against GBS (e.g., ampicillin, penicillin, clindamycin, or erythromycin), additional prophylactic antibiotics are not needed (4).

Neonatal Antibiotics

Another strategy is to give antibiotic prophylaxis to the neonate. Evidence to support this approach initially arose from large retrospective and prospective descriptive series (18). However, a major drawback to this approach is the recognition that the overwhelming majority of neonates with early-onset GBS sepsis are bacteremic at

birth or within 1 hour of delivery (15). Further, in a well-designed trial of low birthweight infants, infants were randomized to receive either 50,000 U of penicillin G within 90 minutes of birth and every 12 hours for 72 hours or only routine newborn care. In the treatment group of 589 infants, ten had GBS bacteremia, and six of these infants died (23). There were 14 cases of GBS bacteremia, with eight deaths among the 598 control patients. Most importantly, bacteremia was present in 90% of treated infants and 86% of controls. This study clearly demonstrated that penicillin prophylaxis in the neonate is ineffective at preventing bacteremia or reducing the mortality rate.

Maternal Vaccination

The ultimate goal of a maternal vaccination strategy for prevention of perinatal GBS disease is to induce protective immunity, both systemically to prevent invasive disease and mucosally to prevent or limit maternal lower genital tract colonization. This strategy has a great appeal from a theoretical perspective. A vaccine would eliminate the problems of screening and intrapartum prophylaxis. It is estimated that maternal vaccination would reduce the number of neonatal GBS sepsis cases by 90% (43). Considerable evidence demonstrates that a maternal vaccination strategy is feasible. Immunization of pregnant women at 31 weeks' gestation with a GBS polysaccharide vaccine resulted in successful transfer of specific functional antibody to the newborn, even though this vaccine preparation was suboptimally immunogenic (44). Even though this strategy hypothetically would prevent most cases of GBS sepsis, as noted earlier, it may not adequately protect prematurely born infants because of inefficient transport of IgG across the placenta (45). An alternative timing of the vaccination may be given to women of childbearing age to avoid hypothetical concerns about vaccination in pregnancy. An additional advantage of a vaccination strategy is that it may reduce maternal GBS infection and potentially GBS-associated premature birth.

It is most likely that the first generation of GBS vaccines to be used in humans will consist of GBS polysaccharides coupled with a carrier such as tetanus toxoid. The seminal work of Lancefield et al. (46) described the capsular polysaccharide (CPS) antigen of GBS as an important target of protective immunity. It has been shown that the lack of circulating CPS-specific IgG correlated with GBS disease among infants born of GBS-colonized women (19). These observations provide the rationale for a GBS vaccine based on CPS, which is surface expressed. Although these native CPS from GBS are safe in adults, they are poorly immunogenic (47). Much recent work has sought to improve the immunogenicity of GBS CPS while maintaining proper antigenicity. Group B streptococcal CPS has been coupled to an immunogenic protein such as tetanus toxoid to form a conjugate. All conjugate vaccines have been superior to the uncoupled vaccines in eliciting a high-titer protective IgG response specific to the serotype in both mice and rabbits (48,49 and 50). Group B streptococcus type III polysaccharide tetanus toxoid vaccine has been shown to be immunogenic in nonhuman primates when administered with an alum adjuvant (51). Accordingly, successful preclinical studies have led to individual phase I and phase II safety and immunogenicity clinical trials with GBS conjugate vaccines for serotypes Ia, Ib, II, III, and V (52,53 and 54), which are the serotypes of major importance in the United States and western Europe. In each trial, the conjugate was shown not only to be safe and well tolerated, but it also elicited higher levels of IgG than did the control uncoupled GBS vaccine. Clearly, a multivalent GBS conjugate vaccine is desirable and offers promise of providing protection simultaneously to both the mother and her

neonate against the most prevalent disease causing GBS serotypes. At the same time, there is considerable interest in GBS proteins as the basis for vaccines. Advantages of protein-based vaccines include the ability to simplify and extend the coverage of the polysaccharides. For example, it is anticipated that a single vaccine containing the type III polysaccharide linked to one of the GBS proteins (such as a C) theoretically could cover the majority of clinically important GBS isolates. A protein-based vaccine also might have reduced toxicity, avoiding overuse of a limited number of existing carrier proteins such as tetanus toxoid. An especially attractive feature of protein-based vaccines is their versatility for use in alternative delivery systems. Unlike polysaccharides, proteins can be incorporated readily into viral, bacterial, or naked DNA vaccines (55). Such developments in vaccines may be of particular importance in eliciting vigorous mucosal immunity. At present, however, there are still major obstacles to vaccine availability. First, the composition of the vaccine for trials has not been established. Second, the maternal antibody response must be IgG (so that the antibodies will cross the placenta), but IgG does not cross well before 32 weeks. Thus, the infants at highest risk for infection would be left with little protection. Third, the timing of vaccine administration (except for the type III polysaccharide) has not been described.

Aftermath Of The 1996 Guidelines

Several years after publication of these guidelines, numerous questions remain. In this section, we will consider areas of potential noncompliance, persisting clinical questions, and persisting policy questions. The CDC guidelines recommend obtaining cultures at 35 to 37 weeks' gestation. If a culture was obtained between 1 and 5 weeks before delivery, sensitivity was 87% and specificity was 97% (56). If a culture was obtained more than 5 weeks before delivery, there was a much greater chance that the results would not accurately predict colonization status at delivery. Compliance with the guidelines requires collection of the culture from the distal vagina and anorectum *and* use of proper laboratory technique. When clinicians do not follow these guidelines, they miss at least one fourth of patients who are culture positive for GBS and who may benefit from antibiotic prophylaxis. The guidelines specifically recommend the use of selective broth medium, which is an enriched medium that enhances the growth of GBS better than agar media and is supplemented with antibiotics to inhibit the growth of organisms other than GBS (57). When selective medium is used, there is a 50% higher rate of GBS detection (58,59). It is consistent with the guidelines to use a nonselective transport medium (such as Amies medium) to transport rectovaginal swabs to the laboratory. It is estimated that in 1998 there was considerable noncompliance in both the site of culture and the use of media. The guidelines recommend penicillin G as the first choice, with ampicillin as the second choice. In penicillin-allergic patients, the recommendation is to use clindamycin or erythromycin parenterally. Group B streptococci are universally sensitive to the penicillins. Because of its narrower spectrum, aqueous penicillin G is the first line drug of choice. As the interval between the first dose of penicillin and birth increases, the proportion of GBS-positive infants delivered from GBS-colonized mothers decreases (Fig. 3.3). When the interval is greater than 2 to 4 hours, few infants are colonized with GBS. It is estimated that there is noncompliance with guidelines in 10% to 20% of cases, even when a policy is in place at an institution. This may be unavoidable, because patients may refuse antibiotics or deliver before antibiotics can be administered (60). In other cases, patients may have barely met the criteria (by having just a few minutes more than 18 hours of membrane rupture or being within a few days of 37 weeks' gestation). These protocols are complex. In one university hospital, the overall noncompliance was 19.7%, but nearly half of these

protocol deviations were due to factors beyond the control of the physician or due to marginal situations (60). Other reports indicate similar rates of noncompliance (61,62).

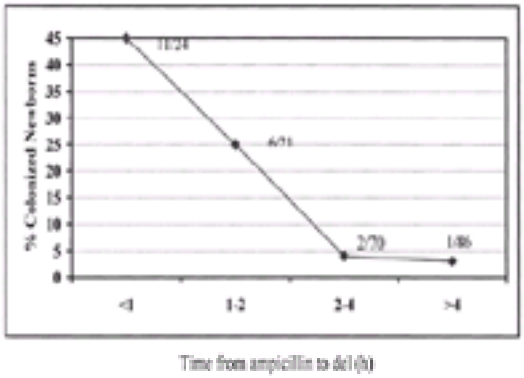

FIGURE 3.3. Timing of intrapartum antibiotic and vertical group B streptococcus transmission. Adapted from ref. 71.

To optimize compliance with protocols, hospitals are encouraged to be proactive, for example, by placing special labels on the chart of GBS-positive patients or instituting a reminder to practitioners on the labor and delivery board as to when a patient becomes at risk.

Is Chemoprophylaxis Necessary For Group B Streptococcus in Elective Cesarean Section?

The current guidelines state that “intrapartum” antibiotics should be given; thus, the guidelines provide no specific recommendations for women admitted for elective cesarean section. The risk of sepsis to the newborn in this situation is low and recently observed to be 0% in an estimated 530 infants at risk (95% CI, 0.0%–0.7%) (63). The number of additional antibiotic exposures is estimated to be about 1% of the total population (assuming that 20% of the population is colonized and the total rate of cesarean section for patients with no labor and no ruptured membranes is approximately 5% of the total obstetric population [i.e., approximately 25% of the total cesarean sections]). Although expert opinion on this issue is divided, a position paper from the Infectious Disease Society for Obstetrics and Gynecology (IDSOG) states that giving GBS antibiotic prophylaxis in this circumstance is not warranted (64).

What Prophylaxis Regimen Should Be Used In Preterm Premature Rupture Of The Membranes Without Labor?

The 1996 guidelines recommend that a GBS culture be collected and then (a) antibiotics given until the culture returns with a negative result or (b) antibiotics given once a positive culture result is available. Several clinical scenarios are not

addressed.

- If the initial culture for GBS is negative, should the culture be repeated? Because the likelihood of a negative antenatal culture becoming positive in the 5 weeks after it was obtained is 5% (56), the IDSOG's position is that it is not necessary to repeat a negative culture for up to 5 weeks in this setting.
- If the initial culture is positive, how long should antibiotics be given? Because this is “antibiotic prophylaxis,” we recommend giving antibiotics intravenously for 48 hours and then obtaining another culture. If the culture remains positive, antibiotics should be given for an additional 5 to 7 days. If the culture at 48 hours is negative, the antibiotic should be discontinued. Patients with preterm PROM should receive *intrapartum* antibiotics according to the guidelines. There is a strong rationale to use broad-spectrum antibiotics to prolong latency with premature PROM from 24 to 32 weeks' gestation (see Chapter 17).

What Prophylaxis Regimen Should Be Used For Preterm Labor That Has Been Arrested With Tocolytics?

The 1996 guidelines recommend that the patient in preterm labor should receive intrapartum antibiotics for GBS prevention, but these guidelines are incomplete. Unless preterm delivery is imminent, we believe that a culture for GBS should be obtained and the mother managed clinically as she would be for preterm PROM. If labor ensues within 5 weeks, the original culture can be relied on; if labor occurs after 5 weeks, a repeat culture should be obtained.

What Is The Threshold Colony Count For Treating Group B Streptococcal Bacteriuria?

Infants born to mothers who are heavily colonized with GBS are more likely to become colonized than are infants whose mothers are lightly colonized (39,65,66). Maternal GBS bacteriuria is a marker for heavy maternal genital colonization. Babies born to mothers with GBS bacteriuria during pregnancy are more frequently and more heavily colonized with GBS (21). In addition, these infants are at increased risk for invasive GBS disease (67,68 and 69).

Moller et al. (70) found GBS bacteriuria in 2.5% of pregnant women screened between 12 and 38 weeks' gestation. There were five cases (7.35%) of confirmed GBS sepsis among 68 infants born to women with GBS bacteriuria compared to none of 2,677 women without GBS bacteriuria (p <0.001) (70).

According to the 1996 guidelines, patients with GBS bacteriuria in the current pregnancy should receive intrapartum prophylaxis, but no definitive threshold colony count for treating GBS bacteriuria prenatally has been established. We recommend treating symptomatic and asymptomatic GBS urinary tract infections according to standards for any other organism. Specifically, treat any patient with $>10^5$ colony-forming units (CFU) per milliliter of urine. If the patient is asymptomatic, treat prenatally if the GBS colony count in the urine is $>10^2$ CFU per milliliter. If the patient is asymptomatic and the colony count is $>10^2$ but $<10^5$ CFU per milliliter, it is prudent to repeat the culture to rule out contamination.

In A Patient With A Negative Screening Culture At 35 to 37 Weeks, Should

Prophylaxis Be Given With Rupture Of The Membranes Greater Than 18 Hours?

It is unlikely that a negative 35-week culture will become positive at term, and the current guidelines do not recommend the use of antibiotics unless the patient has clinical signs of infection. We concur that the low risk of infection does not warrant antibiotics for GBS prevention in this situation.

What Are The Limitations Of The Current Approaches?

The current approaches are complex, and, even when applied perfectly, do not prevent all early-onset disease. One limitation of the current approaches is that an interval of 2 to 4 hours is needed between administration of prophylaxis and reduction in neonatal colonization (71). In addition, the current approaches may not have an impact on late-onset disease and will have no impact on GBS-associated preterm delivery. Further, the major limitation of the risk-based approach is that asymptomatic colonized women at term are not identified. Antimicrobial prophylaxis is not offered to those women, and this approach cannot prevent the estimated 30% to 50% of cases of early-onset GBS sepsis that develop in infants born to women without risk factors (72).

Is Invasive Group B Streptococcal Infection Decreasing In Neonates?

Even before publication of the 1996 guidelines, data from individual hospitals (13,14,31) and larger populations, such as the CDC's multistate surveillance areas (73), demonstrated declining rates of early-onset GBS disease. Rates are lower in geographic areas where more hospitals have prevention policies (74). The CDC's Active Bacterial Core Surveillance (ABCs) now reveals significant declines in early-onset GBS disease in all areas where multiyear data are available. The incidence has declined more than 50% since 1993, compared with no significant decline for late-onset disease or disease in nonpregnant adults, suggesting that intrapartum interventions are responsible for these trends (75). The CDC recently reported the trends in the incidence of GBS disease from 1993 to 1998, based on active population-based surveillance in selected counties in eight states. A case of GBS infection was defined by the isolation of GBS from a normally sterile site. Group B streptococcal disease in infants younger than 7 days old accounted for one fifth of approximately 8,000 GBS infections in these surveillance areas. The overall incidence of early-onset neonatal GBS infection decreased by 65%. In 1993, the rate was 1.7 per 1,000 liveborns; in 1998, it was 0.6 per 1,000 liveborns. The CDC previously had reported an excess of incidence of early-onset disease in black infants compared with white infants. This excess incidence decreased by 75% during this interval. By projecting these findings to the entire United States, it was estimated that 3,900 early-onset GBS neonatal infections, including 200 neonatal deaths, were prevented by use of intrapartum antibiotics in 1998. It also was reported that the incidence of GBS infection among pregnant women declined by 21%. In comparison, the incidence among nonpregnant adults did not decline. This substantial decline in the incidence of GBS infections in newborns, coinciding with implementation of the 1996 guidelines, provides strong evidence that this policy had a major beneficial effect, not only on newborns but also on pregnant women (76). These results are summarized in Fig. 3.4 and Fig. 3.5 (76).

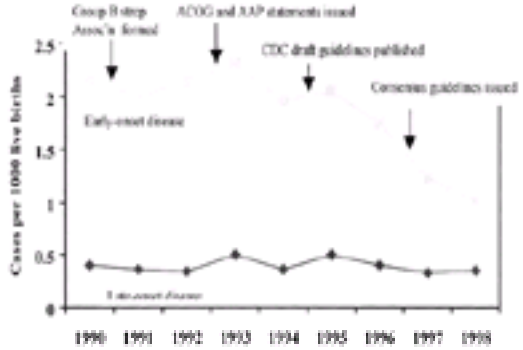

FIGURE 3.4. Incidence of early- and late-onset invasive group B streptococcal disease in three active surveillance areas from 1990 to 1998. Adapted from ref. 76.

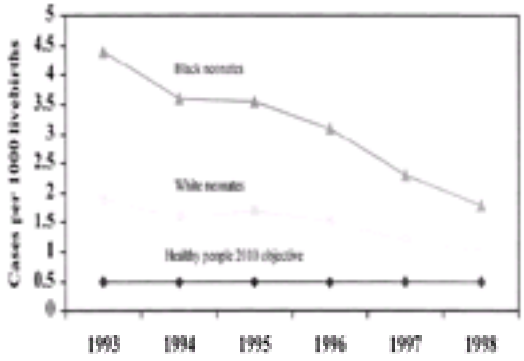

FIGURE 3.5. Incidence of early-onset invasive group B streptococcal disease in black neonates and white neonates in four active surveillance areas, 1993 through 1998. Adapted from ref. 76.

Additional data presented in this report indicate that 9% of cases occurred in infants 33 weeks of age or younger, but the case fatality rate in this gestational age group was 30%. Seven percent of cases occurred in infants between 34 and 36 weeks of age, and the case fatality rate in this group was 10%. Eighty-three percent of cases of early-onset neonatal GBS sepsis occurred among infants 37 weeks of age or older, and the case fatality rate was 2%. Further, the case fatality rate for early-onset neonatal disease (less than 7 days of age) was 4.7% (75/1,584). The case fatality rate for late-onset neonatal disease (7 to 89 days of age) was 2.8% (17/612 cases).

What Adverse Effects Have Occurred From Antibiotic Use?

With up to 25% of gravid women receiving intrapartum prophylaxis, an obvious potential consequence of the use of prophylactic penicillin involves adverse reactions. Mild reactions have been estimated to occur in 1 per 100 uses and

anaphylaxis in 1 per 10,000 uses, but in actual use there have been very few reports of adverse reactions. It is estimated that ten maternal deaths per year would occur if all 1,000,000 GBS-positive gravid women were give intrapartum prophylaxis, assuming fatal anaphylaxis is 0.001% (4).

Are Clindamycin And Erythromycin Appropriate Alternatives for Penicillin-Allergic Patients?

For patients allergic to penicillin, the CDC guidelines recommend clindamycin or erythromycin. Rouse and colleagues (78) reported universal susceptibility of GBS to members of the penicillin family of antibiotics and resistance of 4% of isolates to clindamycin and 21% of erythromycin. Pearlman et al. (79) and Fernandez et al. (80) reported higher resistance rates, with up to 15% of their GBS isolates resistant to clindamycin. These data indicate that infants born to mothers who received clindamycin should be evaluated carefully in the nursery for sepsis. Although cephalosporins are not listed in the CDC guidelines, a first-generation agent might be an acceptable choice for the penicillin-allergic patient without a history of anaphylaxis.

Are Resistant Organisms Being Selected?

Of great concern is whether intrapartum prophylaxis exerts selection pressure toward resistant organisms. In 1993, four cases of non-GBS sepsis cases resulted in death (81). Towers et al. (82) described early-onset neonatal sepsis among 29,897 infants during a 6-year period (Fig. 3.6). During this time, ampicillin use became widespread. Group B streptococcal sepsis decreased over the 6-year duration of the study, whereas non-GBS sepsis increased. These data support the use of penicillin rather than ampicillin as the antibiotic of choice in GBS prophylaxis.

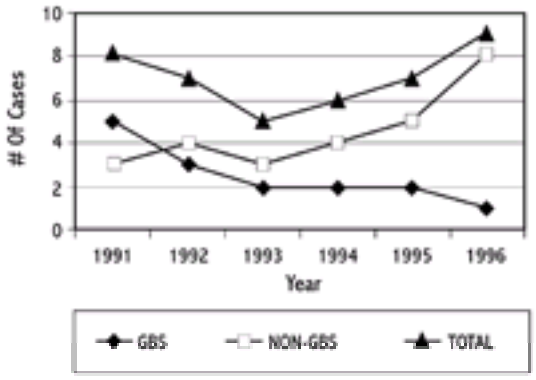

FIGURE 3.6. Early-onset neonatal sepsis. Adapted from ref. 76.

Specific summary recommendations are provided in Box 2, Box 3 and Box 4, which discuss prevention of neonatal sepsis, bacteriuria, and prevention of GBS-related prematurity, respectively.

Box 2

What Should I Do to Prevent Group B Streptococcal Neonatal Sepsis?

- Follow CDC/ACOG recommendations.
- Use penicillin G (5 million U then 2.5 million U q4h) during labor.
- Ampicillin (2 g initially then 1 g q4h) is an alternative.
- In cases of allergy, use erythromycin or clindamycin intravenously.

Box 3

What Should I Do About Group B Streptococcal Bacteriuria?

- Should be treated when detected to prevent symptomatic urinary tract infection.
- Has been associated with preterm birth, and treatment reduces risk.
- Identifies heavy *genital* colonization. Considered an indication for intrapartum prophylaxis to prevent neonatal sepsis.

Box 4

What Should I Do About Group B Streptococcus and Preterm Birth?

- Heavy *genital* GBS colonization is associated with low birthweight infants and preterm birth, but treatment did *not* improve outcome. Group B streptococcal bacteriuria has been associated with preterm birth, and treatment appears to reduce this risk.
- To prevent preterm birth, treat group B streptococcal bacteriuria, but do *not* treat genital colonization prenatally.

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4

GENITAL MYCOPLASMAS

The mycoplasmas are a unique group of microorganisms that commonly inhabit the mucosa of the respiratory and genital tracts (1). Many antigenically distinct species that are infectious in humans have been characterized. These include *Mycoplasma pneumoniae,* the agent responsible for atypical pneumonias, and genital mycoplasmas. The latter consist of *Mycoplasma fermentans, Mycoplasma primatum, Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma urealyticum* (formerly T-mycoplasma or T strains). *Mycoplasma fermentans* and *M. primatum* are uncommon, and there is no good evidence that these organisms produce clinical disease. *Mycoplasma hominis* and *U. urealyticum* are common genital organisms that, over the last 20 years, have been associated with a variety of clinical conditions, including low-birthweight infants, spontaneous abortions, stillbirths, postpartum infections, chorioamnionitis, infertility, and pelvic inflammatory disease. However, the bulk of recent evidence has suggested a more limited role for these ubiquitous genital microbes in the pathogenesis of clinically evident reproductive disorders. *Mycoplasma genitalium* was identified in the early 1980s, initially from men with nongonococcal urethritis. Further evidence strengthens the association between *M. genitalium* and nongonococcal urethritis. There also is support for a role of *M. genitalium* in pelvic inflammatory disease, but *M. genitalium* (unlike *M. hominis* and *U. urealyticum*) is not associated with bacterial vaginosis (2).

Phylogenetically, mycoplasmas fall between bacteria and viruses. All mycoplasmas have several characteristics in common: (a) absence of cell walls, (b) growth in cell-free media, (c) dependence on the availability of sterols for adequate growth, (d) inhibition of growth by specific antibody, and (e) susceptibility of antimicrobial agents that inhibit protein synthesis and resistance to agents that affect synthesis of cell walls. They differ from bacteria because they have no cell wall; rather, a nonrigid triple-layered membrane encloses the cell. Mycoplasmas are the smallest known free-living organisms. They differ from viruses because they contain both DNA and

RNA and because they can grow in cell-free media.

Mycoplasma hominis is distinguished from *U. urealyticum* by differences in colonial morphology, metabolic characteristics, and susceptibility to antibiotics (Table 4.1). *Mycoplasma hominis,* an aerobic organism, is recognizable as a “fried egg” colony. (Fig. 4.1) The organism converts arginine to ornithine with the liberation of ammonia. This reaction produces a color change when an appropriate pH indicator is incorporated into broth media containing arginine. *Ureaplasma urealyticum* is a microaerophilic organism characterized by small colony size and its ability to hydrolyze urea. Urea is an essential substrate for growth and is converted to ammonia. This reaction can be detected by a color change of a pH indicator in broth or agar containing urea.

	Ureaplasma urealyticum	*Mycoplasma hominis*
Colony morphology	Small	Large fried egg
Colony size	20–30 μm	200–300 μm
Metabolic substrate	Urea	Arginine
Aerobic growth	–	+
Antibiotic susceptibility		
Tetracycline[a]	+	+
Erythromycin	+	–
Lincomycin	–	+
Clindamycin	–	+
Penicillin	–	–
Cephalosporins	–	–
Fluoroquinolones	+	+

[a]Tetracycline resistance has been reported for isolates of both *U. urealyticum* and *M. hominis*.

TABLE 4.1. CHARACTERISTICS OF GENITAL TRACT MYCOPLASMAS

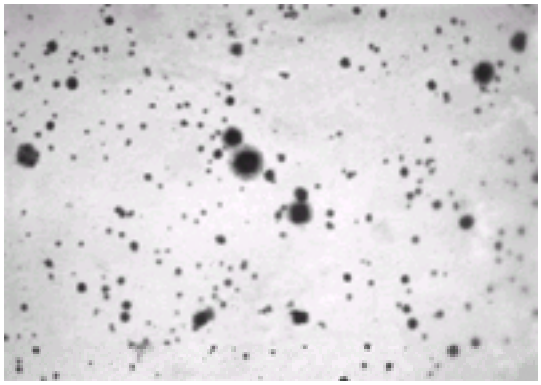


FIGURE 4.1. *Mycoplasma hominis* and *Ureaplasma urealyticum* on a selective agar plate. *Mycoplasma hominis* appears as the larger “fried egg” colonies.

EPIDEMIOLOGY

Infants become colonized with genital mycoplasmas during birth. The organisms are acquired from a colonized cervix or vagina. Approximately one third to one half of newborn females have vaginal colonization with *U. urealyticum,* and a smaller percentage harbor *M. hominis.* A recent review noted that the rate of vertical transmission of *U. ureaplasma* ranges from 18% to 55% for term infants and from 29% to 55% for preterm infants (3). It was further concluded that vertical transmission was not affected by the method of delivery but was significantly increased in the presence of chorioamnionitis. Even when there is cesarean section with intact fetal membranes, colonization of infants with *Ureaplasma* has been well described. Rates of neonatal colonization appear to be highest among very-low-birthweight infants. Mycoplasmas are recovered less frequently from the genital tracts of infant males. Sequential studies have shown a progressive decrease in colonization during the first year of life (4).

Genital mycoplasmas are uncommon in prepubertal girls. After puberty, colonization with genital mycoplasmas occurs primarily through sexual contact. The recovery rate increases dramatically with the onset of sexual intercourse. A wide range in the recovery rate has been reported for *U. urealyticum* (40% to 95%) and for *M. hominis* (15% to 72%) among sexually active women.

Genital mycoplasmas are commonly isolated from gravid women at approximately the same recovery rate as in nonpregnant women with the same degree of sexual activity. Carey and coworkers (5) reported a large study of the epidemiology of *U. urealyticum* in midpregnancy. Demographic variables and other genital isolates were correlated with *Ureaplasma* colonization of the lower genital tract at 26 to 28 weeks in more than 4,900 patients. Representative results are shown in Table 4.2 and Table 4.3. In view of the complex interactions, it is essential to adjust associations of ureaplasmas and adverse outcomes for these confounding factors. Investigations of the role of *M. hominis* and *U. urealyticum* in human disease must take into account this high background prevalence and the complex epidemiology of genital tract mycoplasmas.

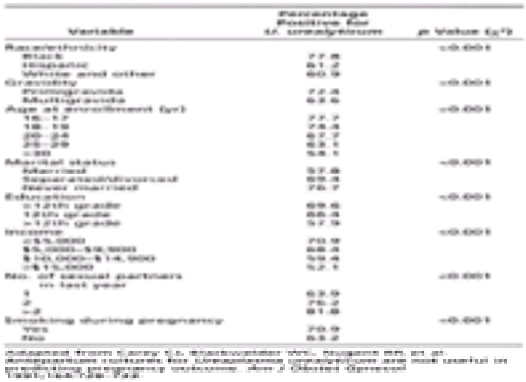


TABLE 4.2. ASSOCIATION OF *UREAPLASMA UREALYTICUM* WITH SELECTED DEMOGRAPHIC VARIABLES

Organism	Percentage Positive for *U. urealyticum*	*p* Value
Trichomonas vaginalis		<0.01
Positive	80.0	
Negative	64.2	
Mycoplasma hominis		<0.01
Positive	85.7	
Negative	58.2	
Neisseria gonorrhoeae		<0.01
Positive	81.5	
Negative	65.6	
Gardnerella vaginalis		<0.01
Positive	75.8	
Negative	64.9	
Bacteroides sp		<0.01
Positive	80.5	
Negative	63.2	
Peptococci		<0.01
Positive	78.3	
Negative	65.1	
Bacterial vaginosis		<0.01
Positive	78.6	
Negative	60.1	

Adapted from Carey CL, Blackwelder WC, Nugent RP, et al. Antimicrobial cultures for *Ureaplasma urealyticum* are not useful in predicting pregnancy outcome. Am J Obstet Gynecol 1991;164:728–733.

TABLE 4.3. ASSOCIATION OF *UREAPLASMA UREALYTICUM* IN THE VAGINA WITH OTHER ORGANISMS

DIAGNOSIS

The diagnosis of mycoplasma infection may be based on isolation of the organism from a site of infection and demonstration of a rise in antibody titer. *Ureaplasma* also may be detected by polymerase chain reaction PCR (6). However, convincing evidence of infection due to genital mycoplasmas often is difficult. Only rarely are these organisms isolated in pure culture, and serologic techniques remain available only as research tools. In women, vaginal specimens are more likely to contain mycoplasmas than are specimens obtained from other sites in the lower genital tract. For optimal isolation of mycoplasmas, specimens should be inoculated immediately into medium, kept at 4°C, and transported to the laboratory as soon as possible.

The basic medium is a beef-heart infusion broth, available commercially as pleuropneumonia-like organism (PPLO) broth, supplemented with fresh yeast extract and horse serum. Antibacterial agents are added to inhibit bacterial growth. The metabolic activity of mycoplasmas can be used to detect their growth in broth medium. Clinical specimens are added to tubes of broth containing phenol red and arginine or urea. *Mycoplasma hominis* metabolizes arginine to ammonia, thus raising the pH of the medium. Ureaplasmas break down urea to form ammonia, resulting in a similar elevation of the pH. Aliquots of the medium from urea broth cultures are subcultured onto agar medium containing urea and manganese sulfate (to detect ammonia); Ureaplasma colonies are dark brown and are inhibited by erythromycin disks. If *M. hominis* is present, an alkaline change occurs in the arginine broth. This broth medium is subcultured on basic PPLO agar containing erythromycin; colonies of *M. hominis* appear in 1 to 4 days and are visualized at 100× magnification. Positive identification of *M. hominis* can be performed by showing inhibition of growth on agar by a paper disk containing anti–*M. hominis* antibodies.

Few clinical laboratories provide cultures for genital mycoplasmas; however, there are few, if any, clinical circumstances when a culture for genital mycoplasmas is clearly indicated.

Various serologic procedures, including agglutination, complement fixation, indirect

hemagglutination, metabolic inhibition test, and enzyme-linked immunosorbent assay (ELISA), have been used to detect serologic response to genital mycoplasmas. In the metabolic inhibition test, specific metabolites (arginine for *M. hominis* and urea for ureaplasmas) are incorporated into broth containing phenol red, organisms, and antibody. The antibody inhibits multiplication and metabolism of homologous organisms, thus preventing a change in color of the pH indicators. With ELISA, specific antibody classes (immunoglobulins G, M, or A) can be detected. In research laboratories, antibody tests for *M. hominis* are considered reliable, but those for *U. urealyticum* seem less so. A significant antibody rise indicates a recent infection but does not demonstrate the site of infection. A PCR technique for detection of *U. urealyticum* was based on nucleotide sequencing of *U. urealyticum* serotype 8. When tested in more than 600 clinical specimens, the PCR technique was equal to, if not more sensitive than, culture for detection of all 14 referenced serotypes of *Ureaplasma.* An advantage of the PCR technique was that results were available within 24 hours compared to the 2 to 5 days necessary for detection by culture. It is anticipated that this research method may be helpful in further determination of the role of ureaplasmas in genital tract infection (6).

CLINICAL MANIFESTATIONS OF GENITAL MYCOPLASMA INFECTION

A summary of the role of genital mycoplasmas in obstetric-gynecologic conditions is given in Table 4.4.

Condition	Evidence Implicating *Mycoplasma hominis*	Evidence Implicating *Ureaplasma urealyticum*
Spontaneous abortion	Weak	Weak
Stillbirth	Weak	Weak
Histologic chorioamnionitis	Weak	Strong
Intraamniotic infection	Strong	Moderate
Neonatal infection, in low birthweight infants	Weak	Strong
Low birthweight/premature birth	Weak	Weak
Postpartum infection	Strong	Strong
Pelvic inflammatory disease	Weak	Weak to none
Pyelonephritis	Moderate	None
Infertility	Weak	Weak

[a]See text for specific data supporting these statements.

TABLE 4.4. SUMMARY OF THE ROLE OF GENITAL MYCOPLASMAS IN OBSTETRIC-GYNECOLOGIC CONDITIONS[a]

Spontaneous Abortion And Stillbirth

Mycoplasmas, both ureaplasmas and *M. hominis,* have been associated with spontaneous abortion since the 1960s. Investigators reported the isolation of genital mycoplasmas from the chorion, amnion, and/or decidua of spontaneously aborted fetuses. However, a causal relationship has not been established. The major unresolved issue is the question of contamination when the products of conception pass through the cervix and vagina. In several studies, mycoplasmas, especially

ureaplasmas, were isolated more frequently from the fetal membranes of fetuses aborted spontaneously than from those aborted therapeutically. Quinn et al. (7) reported a higher rate of lower genital colonization in women with three or more losses than in those with normal fertility (83.3% vs. 25.5%), and Naessens and colleagues (8) found similar differences (64.5% vs. 42.6%). On the other hand, Munday and coworkers (9) found no significant difference and reported a high rate of colonization in both patient groups (67% to 75%). The results of these studies generally suggest that there is an association between spontaneous abortion and maternal or fetal infection, or both, because of genital mycoplasmas. However, it is not clear whether the relationship is causal because of the difficulty in comparing the study groups. Furthermore, the role of other microorganisms was not investigated.

Even though *U. urealyticum* is isolated commonly in amniotic fluid of asymptomatic patients in labor (10), isolation of mycoplasmas from aborted fetuses and stillbirths cannot be explained completely by contamination, as these organisms have been isolated from the lungs, brain, heart, and viscera. Although their presence in the respiratory tract is most likely the result of aspiration of infected or contaminated amniotic fluid, their recovery from heart and viscera probably indicates hematogenous spread, due to either invasion of the fetus through the umbilical vessels or dissemination from infected lungs. However, as noted by Taylor-Robinson and McCormack (1), none of these observations provides an answer to the question of whether abortion occurs because mycoplasmas invade the fetus and cause its death or because the fetus dies of another cause, with subsequent invasion of necrotic tissue by the mycoplasmas.

Because mycoplasmas are sensitive to antibiotics, it is possible that fetal loss, if caused by these organisms, could be prevented by appropriate antimicrobial therapy. Driscoll and coworkers (11) reported successful pregnancies after antibiotic therapy in women who were colonized by ureaplasmas and who had a history of frequent spontaneous abortions. Quinn and colleagues reported antibiotic treatment of 62 couples with histories of pregnancy wastage and with positive genital or urinary cultures for mycoplasmas. Doxycycline treatment before conception reduced the pregnancy loss rate to 48%, compared with a loss rate of 96% in the “no treatment” group. Erythromycin (250 mg four times a day given from the second or third month until the end of pregnancy) further reduced the pregnancy loss rate to 16%, but this trial was small and poorly controlled. These findings have led to the concept that subclinical mycoplasma infection is an important cause of spontaneous abortion, especially repeated abortions. However, these studies did not assess other microorganisms (especially *Chlamydia trachomatis* and anaerobes) that are susceptible to the antibiotic regimens. Most significantly, the effectiveness of antibiotics in preventing spontaneous abortion remains controversial because all the antibiotic trials have been uncontrolled.

The evidence linking genital mycoplasmas to spontaneous abortion is largely anecdotal and unconvincing. Establishment of a causal relationship will require large-scale investigations that assess other potential pathogens and include placebo-controlled trials of antibiotics in patients who had repeat spontaneous abortions.

Histologic Chorioamnionitis

Shurin and coworkers (13) isolated *U. urealyticum* twice as frequently from neonates

whose placentas showed a histologically severe chorioamnionitis than from newborns with less severe or no disease. Because inflammation is related to rupture of the membranes and ureaplasmas are more likely to gain access to the amniotic cavity and colonize the fetus when membranes have ruptured, any association between chorioamnionitis and neonatal colonization may be spurious. Chorioamnionitis could be due to any of the other microorganisms that could gain entry to the amniotic cavity at the same time. The data of Shurin and coworkers are impressive because they controlled for duration of membrane rupture and still noted a statistically significant association between chorioamnionitis and ureaplasmal infection.

In a large, well-designed, case-control study of histologic chorioamnionitis, Hillier and colleagues (14) performed cultures from the area between the chorion and amnion. *Ureaplasma urealyticum* was the most common isolate (47% in preterm cases and 20% in term cases). *Mycoplasma hominis* was isolated much less frequently (8% and 4%, respectively). Results have been similar in other recent microbiologic studies of histologic chorioamnionitis, with *U. urealyticum* being the most common isolate (22% to 28%) and *M. hominis* being isolated in 2% to 4% (15). In a review of the role of *Ureaplasma* and histologic chorioamnionitis, Eschenbach (16) noted that, among five studies, four noted a significant association between isolation of *U. urealyticum* from the chorioamnion and histologic chorioamnionitis.

Clinical Intraamniotic Infection

The role of mycoplasmas in clinically evident intraamniotic infection (IAI; also called amnionitis or amniotic fluid infection) has been of interest (see Chapter 18). In 1983, Blanco and colleagues (10) reported that *M. hominis* was isolated significantly more often in the amniotic fluid of 52 patients with IAI (35%) than in the amniotic fluid of 52 matched controls (8%; $p < 0.001$). In the cases of IAI, *M. hominis* was isolated more often (83% [15/18] of cases) in fluid also containing 102 or more colony-forming units per milliliter of high-virulence bacteria (1). On the other hand, *U. urealyticum* was isolated in half of the fluids of both clinically infected and control patients.

Subsequently, Gibbs and coworkers (17) studied blood culture results for genital mycoplasmas and antibody responses in patients with IAI. *Mycoplasma hominis* was not isolated from the blood of afebrile controls and from only 2% of blood cultures of women with IAI. Even among those women with IAI and *M. hominis* in amniotic fluid, *M. hominis* was isolated in the bloodstream in only 5%. *Ureaplasma urealyticum* was found in the bloodstream more often, but at similar percentages in women with IAI and in controls. Thus, blood cultures shed little light on the role of genital mycoplasmas. To delineate the role of *U. urealyticum* in invasion of the amniotic cavity, Yoon and colleagues (18) studied 120 patients with preterm premature rupture of the membranes (PROM) who delivered preterm neonates within 5 days of amniocentesis. *Ureaplasma urealyticum* was the sole isolate from the amniotic fluid in 21% (21/120) of cases, and *Ureaplasma* was found with other organisms in 9% (11/120). The intrauterine inflammatory response was significantly more intense in patients with positive amniotic fluid cultures limited to *Ureaplasma* than in those with negative culture, as measured by amniotic fluid levels of interleukin-6, tumor necrosis factor alpha, interleukin-1band white blood cell count. Histologic chorioamnionitis also was significantly increased in patients who had *Ureaplasma* only compared to those with negative cultures. The inflammatory response seen in patients with *Ureaplasma* alone was similar to values in patients with positive amniotic fluid

cultures for other organisms or with mixed cultures. These data show that isolation of *U. urealyticum* from the amniotic fluid of patients with preterm PROM is associated with a robust host inflammatory response, suggesting that the organism is not simply a nonpathogen (18).

Serologic response has been more helpful, at least for *M. hominis.* Patients with IAI and *M. hominis* in the amniotic fluid showed a significant antibody response in 85% of cases, whereas women with IAI without *M. hominis* and control women without *M. hominis* in the amniotic fluid showed antibody responses significantly less often. Few asymptomatic women had *M. hominis* in the amniotic fluid. Antibody responses to *U. urealyticum* occurred significantly more often in women with IAI than in controls. However, because there was no correlation between antibody response and isolation and *U. urealyticum* in the amniotic fluid, this response may be viewed as nonspecific or due to *U. urealyticum* in another site (e.g., the vagina). We view these data as supporting a role for *M. hominis* in IAI but leaving the role of *U. urealyticum* still unclear.

Neonatal Infection

Genital mycoplasmas acquired by the term infant during labor generally have not been viewed as a cause of serious infection in most neonates. In 1986, Likitnukul and colleagues (19) in Dallas, Texas, reported the results of blood, urine, and cerebrospinal fluid (CSF) cultures in 203 infants up to 3 months of age with signs and symptoms of sepsis. Proved bacterial infections were diagnosed in 24, including urinary tract infection in 18, bacteremia in four, and meningitis in two. *Mycoplasma hominis* and *U. urealyticum* were not isolated from 199 blood specimens or from 199 CSF specimens, all of which were appropriately tested. Of 170 urine specimens cultured, genital mycoplasmas were isolated in 16 (9.4%), but 12 of these were voided specimens and subject to contamination. The authors concluded that genital mycoplasmas appear to be an uncommon cause of sepsis or meningitis in young infants and that further study is needed to discern their role in urinary tract infection.

Very different information was reported from Birmingham, Alabama, by Waites and coworkers (20), who evaluated CSF cultures in 100 predominantly preterm newborns. *Ureaplasma urealyticum* was isolated in the CSF of eight newborns and *M. hominis* in five newborns who were undergoing evaluation for suspected sepsis or treatment of hydrocephalus. *Escherichia coli* was isolated from the CSF (and blood) of one infant; all other CSF cultures were sterile. These authors noted that the differences found in their study, compared with previous studies, might be explained by (a) their study being limited to newborns; (b) their study involving mainly preterm infants, who may be more likely to be colonized or infected by mycoplasmas; and (c) their maternal population having a high prevalence of genital mycoplasmas (20). *Ureaplasma urealyticum* also has been implicated in chronic lung disease of very-low-birthweight infants. The group in Birmingham reported a significant association between colonization of the respiratory tract of infants weighing less than 1,500 g with *U. urealyticum* and development of bronchopulmonary dysplasia (21). Recent reviews have summarized the role of *U. urealyticum* in both systemic as well as pulmonary infections. There have been well-documented *Ureaplasma* infections of the bloodstream, respiratory tract, and central nervous system of newborns, and it now is accepted that, among preterm neonates, ureaplasmas have the demonstrated ability to produce invasive disease (22). A critical appraisal of four cohort studies examined the association between *U. urealyticum* and chronic lung disease of

preterm infants. Overall, a significant association was found between *Ureaplasma* colonization and chronic lung disease of prematurity (relative risk, 1.91; 95% confidence interval, 1.54–2.37). When infants were stratified by birthweight groupings, no association was observed in infants who weighed more than 1,250 g or among infants weighing less than 750 g. However, the risk of chronic lung disease in the latter group, even among uncolonized infants, was 82% (23). Further evidence has shown an association between *U. urealyticum* and tracheal aspirates and radiographic evidence of bronchopulmonary dysplasia and pneumonia (24).

Low Birthweight And Premature Birth

In early systematic studies of the effects of mycoplasma on infants, workers at Boston City Hospital reported that 22% of infants weighing less than 2,500 g were colonized with *M. hominis* or *U. ureaplasma,* a rate significantly higher than the 12% colonization rate among infants weighing more than 2,500 g (25). In a subsequent study at the same institution, it was reported that 28% of infants with a birthweight of 2,500 g or less were colonized by ureaplasmas, whereas only 5% of those weighing more than 2,500 g were colonized.

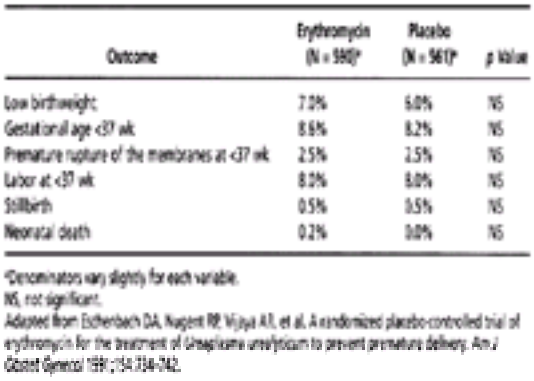
Colonization with mycoplasmas was not associated with other risk factors of low birthweight. Multiple regression analysis indicated that the relation of genital mycoplasmas to birthweight is independent of other variables, such as age, race, parity, and maternal weight. Studies of other authors corroborated the association of low birthweight and mycoplasma colonization. However, in none of 11 cohort studies was an association found between ureaplasmas and low birthweight or prematurity (15).

In the largest study, Carey et al. investigated the associations between *U. urealyticum* colonization at midpregnancy and low birthweight, preterm PROM, or premature delivery (5). From five medical centers in the United States, more than 4,900 pregnant women had vaginal cultures performed at 23 to 26 weeks' gestation and were evaluated for adverse outcomes. Cultures also were obtained for an array of other pertinent microbes. As noted earlier, colonization with *Ureaplasma* was associated with a number of factors, including low maternal age, black race, primigravid status, unmarried status, educational status below grade 12, low income, multiple sexual partners, history of marijuana or cocaine use during pregnancy, and presence of numerous other organisms (Table 4.2 and Table 4.3). Because of the power and size of this study, the authors were able to correct for these confounding variables. After adjustment by multivariate analysis, *U. ureaplasma* colonization at 23 to 26 weeks' gestation was not associated with low-birthweight infants, preterm PROM, preterm labor, or preterm delivery (5).

Controlled antibiotic trials may shed light on the question of pathogenicity of mycoplasmas. In double-blinded controlled studies (conducted before the adverse effect of prenatal tetracycline exposure was recognized), tetracycline was administered to pregnant women (26). In these studies, women treated with tetracycline for 6 weeks gave birth to infants weighing less that 2,500 g statistically less often than did women who were treated with placebo. These studies suggest an effect of the antibiotic therapy on the microbial flora, including mycoplasmas, which resulted in a decreased incidence of low-birthweight infants. In 1980, Kass and colleagues (27) showed an increase in birthweight when women with genital mycoplasmas in the genital tract were treated with erythromycin for the latter half of

pregnancy, compared with women given placebo. However, microbiologic investigations were not conducted to isolate other microorganisms.

In 1991, Eschenbach and coworkers (28) reported a randomized, placebo-controlled trial of erythromycin. Women were enrolled at 23 to 26 weeks' gestation if genital cultures showed *U. urealyticum,* group B streptococcus (GBS), or *C. trachomatis.* A detailed interview and cultures for genital mycoplasmas, aerobes, anaerobes, chlamydia, *Trichomonas vaginalis,* and yeasts were performed. Consenting patients with *U. urealyticum,* GBS, or *C. trachomatis* were randomized to erythromycin base (333 mg twice a day) or placebo. The investigators, in conjunction with a safety committee, decided that the trial should be stopped for women with *U. urealyticum* (but without either GBS or *C. trachomatis*) because of lack of effect. The erythromycin and placebo groups were well matched. Even though the drug of choice for treatment of ureaplasmas was erythromycin, ureaplasmas still were recovered from the vagina of 79% of women in the erythromycin group after 4 weeks of therapy. This rate of recovery was not significantly different from the 84% recovery rate in the placebo group. The authors speculated that the failure of erythromycin to eradicate ureaplasmas was due to the acidic pH of the vagina. Detailed results of this sizable and important study are given in Table 4.5. Although no effect of erythromycin was observed in this investigation, the authors acknowledged that it still was possible for ureaplasmas to cause adverse outcomes. For example, therapy might have to start earlier during pregnancy, or there may be a subset of women “uniquely susceptible” to the effect of ureaplasmas. Further, ureaplasmas were not eliminated from the lower genital tract and thus still may have adversely influenced the pregnancies. However, tissue levels in the upper genital tract should have been sufficient to prevent the organisms from ascending to the uterus where the adverse effects would be initiated. Noncompliance might have led to the absence of effects, but this seems unlikely. Patients had to demonstrate good compliance to enter the trial, and this erythromycin regimen was effective in eradicating other organisms. The authors concluded that erythromycin therapy is not justified for treatment of *U. urealyticum* in the lower genital tract during pregnancy (28). The decreased rate of low birthweight seen in other trials of erythromycin in pregnancy may have been due to an effect on some other organism.



Outcome	Erythromycin (N = 980)*	Placebo (N = 961)*	p Value
Low birthweight:	7.0%	6.0%	NS
Gestational age <37 wk	8.6%	8.2%	NS
Premature rupture of the membranes at <37 wk	2.5%	2.5%	NS
Labor at <37 wk	8.0%	8.0%	NS
Stillbirth	0.5%	0.5%	NS
Neonatal death	0.2%	0.0%	NS

*Denominators vary slightly for each variable.
NS, not significant.
Adapted from Eschenbach DA, Nugent RP, Wiyjya AJ, et al. A randomized placebo-controlled trial of erythromycin for the treatment of Ureaplasma urealyticum to prevent premature delivery. Am J Obstet Gynecol 1991;164:734-742.

TABLE 4.5. RESULTS OF A TRIAL OF ERYTHROMYCIN FOR TREATMENT OF *UREAPLASMA UREALYTICUM* TO PREVENT PREMATURE DELIVERY

Yet another approach to determining the role of an organism in the pathogenesis of preterm birth is to culture for it in the amniotic fluid of women presenting with preterm labor. In ten reports, the rate of amniotic fluid culture positivity varied from 0% to 24% (15). The overall implications of this approach are discussed more fully in Chapter 19. Here we note that genital mycoplasmas have been isolated commonly from the amniotic fluid in this setting when appropriate techniques have been used. For example, Romero and coworkers (29) found positive cultures in 24 (9.1%) of 264 women in preterm labor. Of these 24 women, 6 (25%) were positive for *U. urealyticum* and 4 (17%) were positive for *M. hominis.* Thus, ureaplasmas were isolated from 2.2% of all patients in preterm labor and *M. hominis* from 1.5%. Genital mycoplasmas accounted for two of the three most common isolates (29). In two reports from the University of Washington, isolation of *U. urealyticum* also was common, found in 35% of 13 patients and 46% of 20 patients, respectively, with positive amniotic fluid cultures accounting for 11% and 7% of all patients in preterm labor. Gravett and colleagues (30) noted that women with only genital mycoplasmas in the amniotic fluid did not differ from patients with sterile fluid with regard to time to delivery and response to tocolytics (30,31). Summarizing the role of ureaplasma and premature birth, Eschenbach (16) noted that the presence of *U. urealyticum* in the vagina was not associated with premature birth, and therapy to eradicate ureaplasmas from the vagina during pregnancy did not reduce the incidence of preterm birth. Furthermore, isolation of *U. urealyticum* from the amniotic fluid was not associated with prematurity. However, as noted previously, the recovery of *U. urealyticum* from the chorioamnion has been associated with prematurity and rather consistently with histologic evidence of chorioamnionitis. It was concluded that *U. urealyticum* in the lower genital tract is not associated with preterm birth, but when *U. urealyticum* invades the chorioamnion, it is associated weakly with prematurity and more strongly with histologic chorioamnionitis (16). Cassell and colleagues (32) also have provided a useful review of this topic.

Postpartum Infection

Like other organisms present in the lower genital tract microflora, mycoplasmas can be recovered transiently in the bloodstream following vaginal delivery. McCormack and associates (33) reported that mycoplasmas were recovered from blood cultures obtained a few minutes after delivery from 26 (8%) of 327 women. This bloodstream invasion did not persist and was not associated with postpartum fever (33).

Mycoplasma hominis has been isolated from blood cultures from patients with postpartum fever, and an antibody response was noted in nearly all these cases. McCormack et al. (34) and Wallace et al. (35) recovered *M. hominis* from the bloodstreams of ten febrile postpartum women. In a larger series, Lamey and coworkers (36) isolated bacteria and/or mycoplasmas in 20.8% (26/125) of blood cultures from febrile postpartum women. Genital mycoplasmas were isolated in 12.8% (16/125) of these cultures and from none of 60 afebrile postpartum patients ($p < 0.005$). *Mycoplasma hominis* was isolated in nine blood cultures and *U. urealyticum* in eight. Platt et al. (37) reported an association between a fourfold rise in mycoplasmacidal antibody and fever after vaginal delivery. Genital mycoplasmas are seldom recovered from the blood of postpartum women who are not febrile. Thus, it appears that *M. hominis* causes postpartum fever, most likely by causing endometritis. In general, patients have a low-grade fever for 1 to 2 days and minimal clinical findings, including a mildly tender uterus. They recover uneventfully, even

without specific antibiotic therapy.

The frequency with which endometritis due to *M. hominis* occurs without bloodstream invasion and the percentage of endometritis caused by *M. hominis* are not clear. Recent work suggests that *M. hominis* is a common cause of postpartum infection. However, further studies are needed to elucidate the role of mycoplasmas in postpartum infections, especially in relation to other microorganisms common to the vaginal flora (2).

Pelvic Inflammatory Disease

The role of genital mycoplasmas in pelvic inflammatory disease (PID) is discussed in detail in Chapter 14. Briefly, based on microbiologic and serologic work, *M. hominis* appears to play a role in 10% to 30% of cases of PID (38). Because of the close interaction between *M. hominis* and bacterial vaginosis, these results may reflect the role of vaginosis organisms in the pathogenesis of PID. Overall, the evidence in favor of *M. hominis* outweighs the evidence against it, although it is recognized that the exact proportion of cases of PID attributed to *M. hominis* cannot be specified. The role of *M. hominis* in causing infertility as a consequence of tubal disease also is unknown but there is evidence suggesting a role, as antibody to *M. hominis* has been found three times more often in infertile women who had PID than in controls (2). *Ureaplasma urealyticum* has been isolated only occasionally from the fallopian tubes of women with PID, and experimental efforts to produce salpingitis with ureaplasmas in monkeys have not been effective. Thus, the pathogenic role of ureaplasmas apparently is small, if any (2). *Mycoplasma genitalium,* a recently described genital mycoplasma species, may play a role in PID, and supporting evidence comes from several sources. First, *M. genitalium* adheres to human fallopian tube epithelial cells in culture. In addition, a fourfold or greater rise in specific antibody titer was detected in about one third of women who had acute PID and who did not have evidence of infections due to *Neisseria gonorrhoeae, C. trachomatis,* or *M. hominis.* However, other investigators have not confirmed this finding, leaving the role of *M. genitalium* in PID unresolved at present (2).

Infertility

Some reports have associated ureaplasmas with altered sperm motility or low fertility in males. Cassell et al. (39) assessed 194 women with infertility and found women whose infertility was due to “male” factor were twice as likely to have ureaplasmas in cultures from their lower genital tracts ($p < 0.005$). However, ureaplasmas are about equally common in genital specimens from fertile and infertile persons. For example, Gump and coworkers (40) evaluated 205 women with unexplained voluntary infertility and found no relationship between genital mycoplasmas and numbers or motility of sperm on postcoital test, quality of cervical mucus, and subsequent occurrence of pregnancy.

Small comparative trials of tetracycline in infertile couples showed no support for a role of genital mycoplasmas as an important cause of infertility (1).

Pyelonephritis

Mycoplasma hominis has been isolated from the upper urinary tract in humans only if

there has been acute infection. This isolation also has occurred often when there has been a significant associated antibody response. It is concluded that *M. hominis* is involved in approximately 5% of cases of acute pyelonephritis in humans, especially when there have been predisposing factors such as obstruction or instrumentation.

Whereas *U. urealyticum* has a clear role in nongonococcal, nonchlamydial urethritis in men, there is no evidence suggesting that ureaplasmas are involved in causing pyelonephritis (2).

TREATMENT

Because the mycoplasmas lack cell walls, they are resistant to cell wall-active antimicrobial agents. Thus, the penicillins, cephalosporins, and vancomycin are ineffective. The antimicrobial agents that inhibit protein synthesis are active against most mycoplasmas. In the past, tetracyclines have been uniformly effective against both *M. hominis* and *U. urealyticum.* Tetracycline-resistant isolates of both *M. hominis* and *U. urealyticum* have shown increasing prevalence among clinical isolates. These resistant isolates contain DNA sequences that are homologous to the streptococcal determinant tetM (41). *Mycoplasma hominis* is sensitive to lincomycin but resistant to erythromycin. Ureaplasmas, on the other hand, are sensitive to erythromycin but not to lincomycin. In view of collaborative trial results (5), we must recognize that eradication of ureaplasmas (at least from the lower genital tract) is difficult, presumably because the acidic pH of the vagina inactivates antibiotics such as erythromycin. In addition, *M. hominis* is highly sensitive to clindamycin; ureaplasmas are moderately sensitive to clindamycin. The aminoglycosides have some activity against mycoplasmas. In view of recognized tetracycline-resistant isolates of genital mycoplasmas, tetracyclines can no longer be expected to be a universally effective treatment. In those rare circumstances where specific antibiotic therapy is aimed at *M. hominis,* clindamycin may be used as an alternative, especially when there is no response to tetracyclines. In circumstances where treatment is aimed specifically at ureaplasma infections, mainly in nongonococcal urethritis in men, erythromycin or fluoroquinolones can be used in those circumstances where there is no response to tetracycline (41).

Because of the still unproved causal relationship with genital disease, indications in obstetrics and gynecology for directing therapy at genital mycoplasmas are rare. Treatment of patients with repeated abortions, premature labor, or unexplained infertility should be considered experimental. In clinical conditions in which *M. hominis* seems to play a true role, such as IAI or puerperal fever, good clinical responses usually are seen even with antibiotics having poor activity against *M. hominis.*

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5

CHLAMYDIAL INFECTIONS

Chlamydia trachomatis is the most common sexually transmitted bacterial organism in the United States. It is estimated that more than four million new cases of infection occur each year, at an estimated cost of $2.4 billion (1,2,3,4,5,6,7 and 8). In the United States, chlamydial infection is the most commonly reported infectious disease (3). In 1998, there were 604,420 cases of chlamydial infection reported to the Centers for Disease Control and Prevention (CDC) (9). Worldwide, *C. trachomatis* is also the most common sexually transmitted bacterial pathogen, with an estimated 90 million new cases annually (10). Washington et al. (5) estimated that more than three fourths of the health care costs associated with chlamydial infection in the United States involve women (5). Of most concern is the recognition that the health consequences of chlamydial infection are greatest for women (7). In large part, this results from the increased risk of women infected with *C. trachomatis* to develop pelvic inflammatory disease (PID) and its sequelae of tubal factor infertility, ectopic pregnancy, and chronic pelvic pain (2,11). Additionally, pregnant women infected with *C. trachomatis* but who are untreated are at increased risk for adverse pregnancy outcome, including preterm delivery, premature rupture of the membranes (PROM), and low birthweight infants (7,12). Infants born to mothers with untreated chlamydial infection of the cervix are at increased risk to develop neonatal conjunctivitis and/or pneumonia (13). Moreover, women infected with *C. trachomatis*

appear to be at increased risk to acquire human immunodeficiency virus infection (14,15 and 16).

During the past 20 years, the spectrum of diseases caused by *C. trachomatis* has expanded dramatically, and an increasing number of infections have been attributed to *C. trachomatis* (Table 5.1) (1,6,8,17,18,19 and 20). As noted by Stamm (6), many of these clinical syndromes closely resemble the infections associated with *Neisseria gonorrhoeae.*

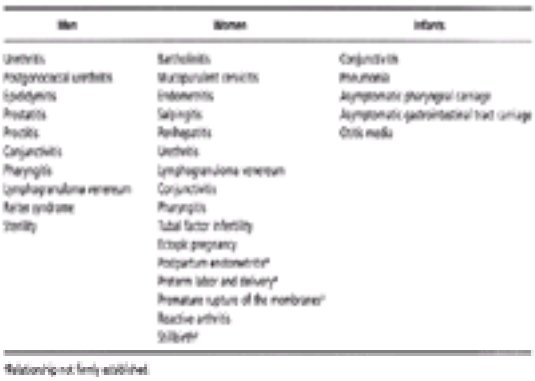


TABLE 5.1. CLINICAL SPECTRUM OF *CHLAMYDIA TRACHOMATIS* INFECTIONS

Chlamydia trachomatis has long been known as the causative agent of trachoma, a disease that is hyperendemic in many developing countries and considered to be the leading preventable cause of blindness in the world (8,21). Schachter (8) has estimated that trachoma affects 400 million people living in areas endemic for the disease. An estimated six million people have been blinded as a result of trachoma (22). In addition, chlamydia is the pathogen long known to cause inclusion conjunctivitis in the newborn and lymphogranuloma venereum (LGV). Since the early 1980s, chlamydial infections of the genital tract and the consequences of perinatal exposure, both maternal and neonatal, have received considerable attention (23). More recently, attention has focused on the adverse effects on reproductive health associated with the sequelae of upper genital tract infections with *C. trachomatis* in women (1). In particular, chlamydial infection appears to play a major role in asymptomatic, atypical, or unrecognized syndromes of PID (1,24).

Although *C. trachomatis* affects and causes important diseases in men, women, and infants, this review will focus primarily on the genital tract disease associated with chlamydial infections in women and in the newborn. Women bear the brunt of the chlamydia burden because of their increased risk for adverse reproductive consequences. With the increasing awareness of the role of *C. trachomatis* as a sexual pathogen has come an increased awareness by clinicians of the chlamydia problem. *Chlamydia trachomatis* is a high-prevalence agent and is associated with a wide variety of complications. Unfortunately, the majority (50% to 70%) of chlamydial infections of the lower genital tract in women are asymptomatic and can progress into the upper genital tract to produce serious complications, such as PID, tubal

factor infertility, and ectopic pregnancies (1,20). Other long-term consequences of chlamydial infection include neonatal conjunctivitis and chlamydial pneumonia of the newborn. Association of the chlamydial infection with fetal wastage, PROM, preterm labor and/or delivery, and postpartum endometritis has been suggested.

Cates and Wasserheit (1) suggested that the failure to control chlamydial infections and the resultant increased incidence of these infections can be attributed to several factors: (i) nonspecific signs and symptoms of chlamydial infection; (ii) mild or absent signs and symptoms of chlamydial infection; (iii) inadequate laboratory facilities for detection of *C. trachomatis*; (iv) expense and technology associated with testing for *C. trachomatis*; (v) clinicians' lack of familiarity with chlamydial infections; (vi) need for at least 7 days of multiple-dose therapy (until very recently); and (vii) inadequate resources directed at screening high-risk patients, tracing contacts, and treating partners. As a result of these factors, early diagnosis and compliance with treatment are less likely to occur with chlamydial infections than with other bacterial sexually transmitted diseases (STDs), such as gonorrhea and syphilis.

THE ORGANISM

There are four recognized species within the genus *Chlamydia: C. trachomatis, C. psittaci, C. pneumoniae, and* C. pecorum. The properties of these *Chlamydia* sp are given in Table 5.2.

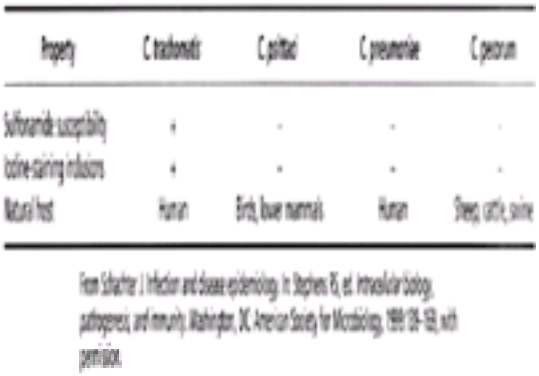


TABLE 5.2. PROPERTIES OF *CHLAMYDIA* SPECIES

Chlamydia psittaci is the causative agent of psittacosis, a common pathogen in avian species and lower mammals. Human *C. psittaci* infections are rarely found in the United States. *Chlamydia pneumoniae* (TWAR) is a recently identified third species in the genus *Chlamydia* that causes acute respiratory tract infections (25,26). Initial reports describing this organism referred to TWAR as a strain of *C. psittaci* that was a human pathogen associated with respiratory tract infections (25). Subsequent studies demonstrated that there is less than 10% DNA homology between TWAR and strains of *C. psittaci* and that the TWAR elementary body has a pear shape with a periplasmic space, unlike the round elementary body with little or no periplasmic space associated with *C. psittaci* and *C. trachomatis.* As a result, *C. pneumoniae*

was classified as a new species (26). The clinical syndromes associated with *C. pneumoniae* infection include bronchitis, pneumonia, otitis, pharyngitis, and sinusitis (26). It has been suggested that *C. pneumoniae* may play a role in coronary artery disease (27,28). In the Finnish studies, patients with coronary artery disease were shown to have high levels of antibody to *C.pneumoniae* (27,28). Kuo et al. (29) detected chlamydial antigen and genes in atherosclerotic lesions of coronary arteries. *Chlamydia pecorum* is a recently recognized species that formerly was a subset of *C. psittaci* (30,31). *Chlamydia pecorum* appears to cause disease in the reproductive tract of sheep, cattle, and swine (8,32). *Chlamydia trachomatis* seems to be a specifically human pathogen (except for a few strains of rodent origin). *Chlamydia psittaci* is differentiated from *C. trachomatis* on the basis of sulfonamide resistance and failure of inclusions to stain with iodine. *Chlamydia trachomatis* is sensitive to sulfonamides and has iodine-staining inclusions. *Chlamydia pneumonia* is not sensitive to sulfa drugs. The associations of *Chlamydiae* sp and human disease are summarized in Table 5.3.

Species	Serotype	Disease
Chlamydia psittaci	Many	Psittacosis
Chlamydia pneumoniae	TWAR	Acute upper and lower respiratory tract infections
Chlamydia trachomatis	A, B, Ba, C	Hyperendemic blinding trachoma
	D, E, F, G, H, I, J, K	Inclusion conjunctivitis, nongonococcal urethritis, proctitis, epididymitis, cervicitis, endometritis, salpingitis, pneumonia of newborn
	L1, L2, L3	Lymphogranuloma venereum

TABLE 5.3. CHLAMYDIAE: TAXONOMY AND ASSOCIATION WITH HUMAN DISEASE

Although all chlamydiae share a common genus-specific antigen (chlamydial lipopolysaccharide), *C. trachomatis* may be differentiated further on a serologic basis. There are currently 15 recognized serotypes (Table 5.3). The *C. trachomatis* serotypes are responsible for three major groups of infections. Three of these serotypes (L1, L2, L3) represent the agents causing LGV. Lymphogranuloma venereum appears to have different receptor sites and a much broader tissue spectrum *in vivo* and host spectrum *in vitro* than the other *C. trachomatis* strains. In addition, the LGV serotypes are more invasive than the other chlamydial serotypes. Serotypes A, B, Ba, and C are the agents responsible for endemic blinding trachoma. The remaining serotypes of *C. trachomatis* (D, E, F, G, H, I, J, K) are the oculogenital and sexually transmitted strains that cause inclusion conjunctivitis, newborn pneumonia, urethritis, cervicitis, epididymitis, salpingitis, acute urethral syndrome, and perinatal infections.

The chlamydiae are separated into their own order (Chlamydiales) and family (Chlamydiaceae) on the basis of a unique growth cycle (Fig. 5.1) that distinguishes them from all other microorganisms (8,19,33,34). This growth cycle involves infection

of a susceptible host cell via a chlamydia-specific phagocytic process by which chlamydiae are preferentially ingested (35,36). Subsequent to attachment and phagocytosis, chlamydiae remain in a phagosome throughout the growth cycle; surface antigens of chlamydiae are believed to inhibit phagolysosomal fusion (37). The chlamydial organism exists in two forms: (i) the elementary body, which is the infectious particle capable of entering uninfected cells; and (ii) the reticulate body, which multiplies by binary fission to produce the inclusions that are identified in properly stained cells.

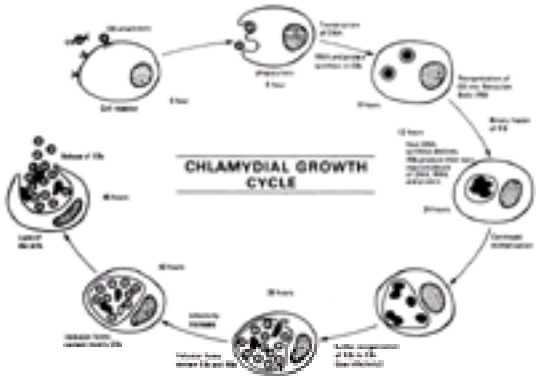


FIGURE 5.1. Chlamydial growth cycle. EB, elementary body; RB, reticulate body. (From Thompson SE, Washington AE. Epidemiology of sexually transmitted *Chlamydia trachomatis* infections. *Epidemiol Rev* 1983;5:96–123, with permission.)

Schachter (33) has noted that the life cycle of chlamydiae can be divided into several steps: (i) initial attachment of the elementary body (infectious particle) to a host cell; (ii) entry into the host cell; (iii) morphologic change into the reticulate body with subsequent intracellular growth and replication; (iv) transformation of the reticulate bodies into the elementary bodies; and (v) release of the infectious elementary bodies.

Initiation of infection depends on what appears to be specific attachment sites on susceptible host cells (35). The initial step in this process is attachment of the metabolically inactive but infectious elementary body to a susceptible host cell. This probably involves a specific receptor-ligand interaction (33). Attachment is mediated by heparin sulfate-like molecules (38). The host cells are generally nonciliated columnar or cuboidal epithelia, such as those found in the conjunctiva, urethra, endocervix, and mucosa of the endometrium and fallopian tubes. After the elementary body attaches to the host cell, it is rapidly ingested by a phagocytic process similar to ordinary bacterial phagocytosis (36). This process is an enhanced phagocytosis that is induced by the elementary body, which then is selectively taken up by the susceptible host cell. Entry of chlamydia appears to occur via a mechanism similar to receptor-mediated endocytosis (39). Intracellularly, the elementary bodies exist within a cytoplasmic vacuole. Chlamydiae remain within this phagosome throughout their entire growth cycle. In this state, chlamydiae may be protected from host defense mechanisms, such as cellular lysosomes. Schachter (33) has suggested that these two characteristics, induced phagocytosis and prevention of

phagolysosomal fusion, are major virulence factors of chlamydia. In the next step of the chlamydia growth cycle, the elementary body, approximately 8 hours after entry, undergoes reorganization into what is called a reticulate or initial body, which represents the metabolically active and dividing form of the organism. These forms are not infectious and will not survive outside the cell. They divide for approximately 8 to 24 hours and then condense and reorganize to form new elementary bodies. For their entire intracellular life, the chlamydiae reside within the phagosome, but they successfully prevent phagolysosomal fusion (33). Chlamydiae are detected by recognition of their characteristic cytoplasmic inclusions. Infectivity increases as the number of elementary bodies increases. By 48 to 72 hours, the host cell bursts and liberates these infectious particles, or the inclusion is extruded intact by a process of reverse endocytosis. The cycle then starts anew. The complete infectious cycle takes approximately 48 to 72 hours.

Chlamydia trachomatis is an obligatory intracellular bacterium (8,33). It is an extremely well-adapted human parasite that depends on the host cell for nutrients and energy (33). Although chlamydiae are capable of limited metabolic activities, they do not possess an enzyme system capable of generating ATP and have been considered energy parasites. Although chlamydiae do not stain with the Gram stain, in many respects they are like bacteria. They contain DNA and RNA, are susceptible to certain antibiotics, have a rigid cell wall, are similar in structure and content to Gram-negative bacteria, and multiply by binary fission. They differ from bacteria but are similar to viruses in that they are obligate intracellular parasites. They may be regarded as bacteria that have adapted to an intracellular environment; thus, they need viable cells for their multiplication and survival.

Chlamydiae also differ from Gram-negative bacteria because they lack the peptidoglycan layer that resides between the outer and inner membranes of bacterial cell walls and provides shape and rigidity to bacteria (40). However, elementary bodies are rigid, and their resistance to physical disruption is due to covalent disulfide linkages among outer membrane proteins (41). The outer membrane proteins involved in the disulfide linkage are the major outer membrane proteins (MOMP), with molecular weight of 60,000, and a 12,000 molecular weight dalton cysteine-rich protein (42). In addition to its role in maintaining the structural integrity of *C. trachomatis*, the MOMP is a transmembrane protein that functions as a porion that allows for ingress and egress of low-molecular-weight substances such as sugars and some antibiotics (43). Chlamydiae also contain a lipopolysaccharide (LPS) similar to that present in the outer membrane of Gram-negative bacteria (44).

EPIDEMIOLOGY AND TRANSMISSION

Chlamydia trachomatis (serotypes A, B, Ba, C) has long been recognized as the causative agent of trachoma, a chronic conjunctivitis affecting an estimated 400 million people in developing countries and resulting in millions of cases of blindness. In trachoma endemic areas, child-to-child transmission is the most common method of chlamydial transmission (33). Spread of chlamydial organisms is facilitated by poor hygiene and unsanitary conditions (33). However, the child-to-child and intrafamilial patterns of infection in trachoma endemic areas are not applicable to the clinical manifestation of infections associated with the oculogenital *C. trachomatis* strains (serotypes D, E, F, G, H, I, J, K).

For these oculogenital serotypes, which are the major focus of this chapter, the

primary method of transmission is sexual. Schachter (19,33) has stated that *C. trachomatis* is probably the most common sexually transmitted bacterial pathogen in western industrialized society. *Chlamydia trachomatis* appears to be more difficult to transmit than *N. gonorrhoeae* (45,46). Katz et al. (45) used extrapolations from partner notification programs within couples with discordant infection status and estimated that male-to-female transmission of chlamydia occurs 40% of the time and female-to-male transmission 32%. Quinn et al. (46) used polymerase chain reaction (PCR) rather than culture and suggested that transmission from men to women and from women to men may be equally efficient. Lycke et al. (47) studied partners of men with chlamydial or gonococcal urethritis and noted that female partners were infected 45% and 80% of the time, respectively.

Chlamydiae cause between one third and one half of nongonococcal urethritis (NGU) cases in men (48,49). Double infections with gonococci are common in both men and women. Between 20% and 40% of men and between 30% and 50% of women with lower genital gonorrheal infection have concomitant chlamydial infection (6,48,49 and 50). Men with gonorrhea treated with penicillins frequently develop postgonococcal urethritis due to concomitant chlamydial infection. Epididymitis is an important complication of chlamydial infection of the male urethra (51), and *C. trachomatis* is the major cause of epididymitis in men under the age of 35 years. Rectal and pharyngeal infections also occur in both sexes (6). Reiter syndrome is a systemic clinical syndrome associated with chlamydial infection in men.

A number of clinical conditions in the female have been attributed to *C. trachomatis* (6,8,19,22). These include mucopurulent endocervicitis, endometritis, salpingitis, acute urethral syndrome, urethritis, and perinatal infections. The anatomic site within the female genital tract most commonly infected with *C. trachomatis* is the cervix. Unfortunately, there are no specific symptoms associated with the cervical infections; thus, many of the chlamydial infections of the cervix are clinically inapparent. This is unfortunate, because mucopurulent cervicitis (MPC; the female equivalent of NGU) caused by *C. trachomatis* predisposes to acute PID in nonpregnant women and to maternal and infant infections during pregnancy. In addition, asymptomatic chlamydial cervicitis is a major reservoir for sexual transmission of *C. trachomatis.*

Until recently, genital chlamydial infection was not a reportable disease in the United States. Physician surveys and sentinel surveillance projects were used to estimate national trends (1). Since the early 1970s, chlamydial infections have been more common than gonococcal infection in the United States (1). Washington et al. (52) developed a model that used the ratio of chlamydial to gonococcal infections to estimate the annual incidence of genital chlamydial infection. These authors estimated that in 1986 there were nearly 4.5 million chlamydial infections in the United States, with 2.6 million occurring in women, 1.8 million in men, and 250,000 in infants. In 1996, chlamydia became a notifiable disease. By 1998, there were 604,420 cases of chlamydia reported to the CDC (236 cases per 100,000), making chlamydia the most frequently reported infection in the United States (3,53). The annual incidence of new chlamydial infections in the United States is estimated to be over four million cases (8,33,54). However, as noted by Schachter, reporting for chlamydia remains fragmentary, screening is sporadic among various populations, and testing for chlamydia is inadequate (e.g., culture or antigen detection vs. nucleic acid amplification tests) (8). As a result, it is likely that these data underestimate the true incidence of chlamydial infection in the United States. Of the reported U.S. cases, 82% occurred in women and 73% occurred in the 15- to 24-year-old age

group (53). These reported rates for women are an overestimate of the female-to-male ratio of chlamydial infection, because women are much more likely to be screened (8). Chlamydial infections are present through all strata of society, but the highest rates occur in the young and the poor (8). As noted by Stamm (6), in areas where intensive chlamydia control programs have been instituted, dramatic decreases in the prevalence of chlamydia have occurred. Such has been reported in Sweden, where the number of cases of chlamydial infection decreased more than 50% from 1987 to 1994 (55) and in selected areas of the United States (e.g., the Pacific Northwest and Wisconsin), where similar results have been reported (4,56,57).

Many sexually active women have been exposed to chlamydiae. The prevalence of serum antibody to *C. trachomatis* increases with age until about 30 years, when it plateaus at approximately 50% (6). Most women with antibody titers against chlamydia do not have a current infection. In general, *C. trachomatis* is isolated from the cervices of between 3% and 5% of unselected asymptomatic nonpregnant women. The prevalence of chlamydial infection depends on the population of women screened (1,2,4,7,19,20,58); in selected populations, *C. trachomatis* is more prevalent. *Chlamydia trachomatis* has been recovered from 15% to 33% of patients examined in STD linics (59,60,61,62 and 63), 29% to 68% of female partners of men with NGU (48,61,64,65,66 and 67), 67% to 74% of female partners of men with culture-positive *C. trachomatis* urethritis (48,64,67), and 28% to 63% of women with mucopurulent endocervicitis (68,69 and 70). In family planning clinics, 2.8% to 9.4% of asymptomatic women were positive for *C. trachomatis*(4,71,72 and 73). Among asymptomatic women attending gynecology clinics, female college students, and women attending primary care clinics, the prevalence of chlamydial infection generally ranges from 3% to 5% (74,75,76,77,78 and 79). In a large community-based screening study using urine ligase chain reaction (LCR), the overall prevalence of chlamydia in young women was 8.6% (80). Among female military recruits, the prevalence of chlamydial infection has ranged from 8.2% to 9.8% (81,82 and 83). Adolescents are the population considered to be at highest risk for chlamydial infection; the prevalence of cervical chlamydial infection in adolescent women is generally greater than 10%, with rates as high as 40% reported (84,85,86,87,88 and 89). Among pregnant women, the prevalence of chlamydial cervical infection has ranged from 2% to 37% (90,91,92,93,94,95,96,97 and 98), with 5% to 7% of pregnant women generally culture positive.

Whereas 3% to 5% of sexually active women in the United States carry chlamydia in their cervices, high-risk populations can be readily identified. A number of studies have shown that the same populations that are at risk for other sexually transmitted infections are at highest risk for chlamydial infections. A number of patient characteristics have been found to be predictors of chlamydial genital infections (6,8,63,85,99,100). These include young age, socioeconomic status, nonwhite race, number of sexual partners, new partner, and oral contraceptive use. Chlamydial infection rates are inversely related to age (Fig. 5.2) (1,6,8,71,101) and directly related to the number of sexual partners (78,101,102). Lower socioeconomic status has been associated with an increased risk for chlamydial infections (71,101,102). Young women using oral contraceptives are at greater risk for cervical chlamydial infection than women using other methods of contraception (61,64,103). Risk factors for chlamydial cervical infection in pregnant women include unmarried status, age less than 20 years, presence of other STDs, residence in inner city ghettos, seeking prenatal care late, having a partner with NGU, presence of mucopurulent endocervicitis, and abacteriuric pyuria. Handsfield and coworkers (104) described

characteristics that are predictive of chlamydial infection in women attending a family planning clinic. These include age less than 24 years, a new sexual partner within the preceding 2 months, mucopurulent cervical discharge, bleeding easily induced by swabbing the endocervical mucosa, and use of no contraception or a nonbarrier method. Additional high-risk groups include women with cervical ectopy (60,64,67,105) and women who are partners of men with NGU (48,61,64,65,66 and 67). Stergachis and coworkers (106) assessed the prevalence of cervical infection with *C. trachomatis* in a population-based study of nonpregnant women 15 to 34 years of age attending primary care clinics at Group Health Cooperative of Puget Sound (106). Based on multivariate logistic regression, seven patient characteristics were independently predictive of chlamydial infection: (i) being unmarried; (ii) cervical ectopy; (iii) black race; (iv) douching; (v) nulliparity; (vi) age 24 years or younger; and (vii) intercourse with two or more partners within the preceding year. Hillis et al. (107) evaluated risk factors for recurrent chlamydial infection in women using the Wisconsin Sexually Transmitted Disease Surveillance System. Young age at first reported infection was the strongest predictor of recurrent infection; age younger than 15 years had an eightfold increased risk, age 15 to 19 years old had a fivefold increased risk, and age 20 to 29 years old had a twofold increased risk compared with women 30 to 44 years old (107). Other characteristics associated with an increased risk of recurrence included black race, urban residence, coinfection with gonorrhea, and past STDs (107).

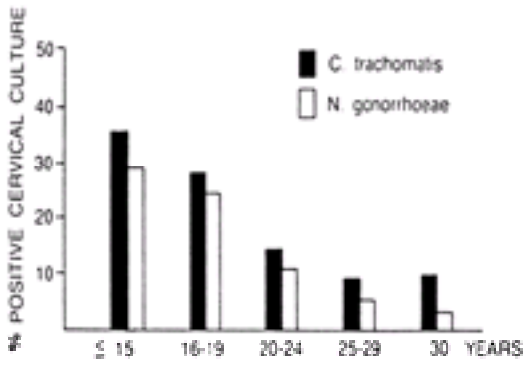


FIGURE 5.2. Prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* cervical infection by age in women attending a sexually transmitted disease clinic. (From Stamm WE. Chlamydia trachomatis infections of the adult. In: Holmes KK, Sparling PF, Mardh P-A, et al., eds. *Sexually transmitted diseases.* New York: McGraw-Hill, 1999:407–422, with permission.)

The majority of women with chlamydial disease remain untreated because their infection is either asymptomatic or relatively inapparent. In general, one half to two thirds of chlamydial infections of the cervix are asymptomatic (6,8,71). If the infection is not treated, it can persist for several years and subject those infected to the risk of spread of *C. trachomatis* to the upper genital tract, with subsequent infertility and ectopic pregnancy (2,19).

More than one million women in the United States acquire PID each year. Both

medically and economically, PID is the most important genital disease caused by *C. trachomatis* (8). Studies in the United States suggest that 20% to 50% of these cases are associated with *C. trachomatis* (108,109 and 110). Thus, 200,000 to 500,000 cases of chlamydia-associated PID occur annually in the United States and are estimated to require 50,000 to 100,000 hospitalizations each year. These women are exposed to significantly increased risk for infertility and ectopic pregnancies. The implications of these data are discussed in greater detail in Chapter 14.

The infant born to a woman with chlamydial infection of the cervix is at 60% to 70% risk to acquire the infection via vertical transmission during passage through the birth canal (90,91,92,93 and 94). Approximately 25% to 50% of exposed infants will develop chlamydial conjunctivitis in the first 2 weeks of life, and 10% to 20% of the infants will develop chlamydial pneumonia within 3 to 4 months of birth. In addition, women with undetected cervical infection are a reservoir for horizontal transmission to their sexual partner(s). These significant complications associated with vertical transmission to newborns, horizontal transmission to partners, and ascending genital tract infection with *C. trachomatis* strongly demonstrate the need for large-scale screening programs to detect cervical chlamydial infections. When such chlamydia control programs have been undertaken, a dramatic impact on lowering the rate of genital chlamydial infection has occurred (55,56 and 57).

Chlamydial infections are common among men (2,6,8). Unlike in women, chlamydial infections in men rarely result in sequelae (2). However, infected (especially asymptomatic) males serve as a reservoir for infecting their sex partner(s) and exposing them to the significant sequelae associated with chlamydial infection in women. The prevalence of chlamydial urethritis in men attending general medical clinics, adolescent clinics, student health services, and STD clinics has ranged from 3% to 5% of asymptomatic men screened in general medical clinics to 15% to 20% of men screened in STD clinics (6,19,111). Among sexually active male adolescents attending adolescent clinics, 13% to 15% rates of chlamydial urethral infection have been reported (112,113). Similar to women, there is a striking inverse relationship between age and prevalence of *C. trachomatis* infection among men (6). Epididymitis is a severe complication of acute urethritis. Approximately 50% of the 500,000 cases of epididymitis occurring annually in the United States are caused by *C. trachomatis* (51). In homosexual men who practice receptive anal intercourse without condom protection, *C. trachomatis* is a cause of acute proctitis (114,115 and 116). Pharyngeal infection with chlamydia occurs in men and women with recent orogenital contact (117). Reiter syndrome (urethritis, conjunctivitis, arthritis, and characteristic mucocutaneous lesions) and sexually acquired reactive arthritis (SARA) have been associated with *C. trachomatis* (6,8). It is estimated that Reiter syndrome occurs in 1% to 2% of NGU cases in Europe (8). Sexually acquired reactive arthritis, without the classic triad of Reiter syndrome, is an even more frequent complication of NGU (118).

CLINICAL SPECTRUM OF CHLAMYDIAL INFECTION

Chlamydial Infection In Men

Chlamydia trachomatis has been recovered from multiple sites in the male anogenital tract. These sites include the urethra (19,48,49 and 50), epididymis (51,119), prostate (119,120), and rectum (114). The prevalence of chlamydial urethral infection in asymptomatic men in general medical settings is 3% to 5% (6).

In STD clinics, 15% to 20% of men are infected with *C. trachomatis* (2,6,8,19). Considerable data have been presented over the past 20 years demonstrating that *C. trachomatis* is a primary pathogen in infections involving these sites.

Urethritis

Chlamydia trachomatis is a major cause of NGU (6,8,19,48). Investigations have shown that *C. trachomatis* can be isolated from 26% to 72% of men with NGU; most investigators report isolation of *C. trachomatis* in 25% to 50% of NGU (6,8,50,109). In the United States, the CDC estimates that 1.2 million to 2.4 million physician visits for chlamydial urethritis (2) are made annually.

Diagnosis of NGU is made in men who complain of dysuria, frequency, or discharge, or who have urethral discharge on examination; who are found to have an abnormal number of polymorphonuclear leukocytes (PMNs) in the urethral discharge or first-void urine specimen; and who do not have the typical Gram-negative intracellular diplococci suggestive of gonorrhea or a culture positive for gonorrhea. The generally accepted definition of NGU is based on the presence of ³5 PMNs per oil immersion field of an intraurethral swab in the absence of gonococci (20). However, men can harbor *C. trachomatis* in their urethra in the absence of symptoms or have fewer than 5 PMNs on Gram stain (20,111). Establishing that NGU is due to *C. trachomatis* requires chlamydial isolation, use of antigen detection methods such as monoclonal antibody staining of direct smears or immunoassay (enzyme-linked immunosorbent assay), or use of DNA amplification tests such as PCR, LCR, or transcription-mediated amplification (TMA) (6). Leukocyte esterase test to screen urine for evidence of urethritis (gonococcal and/or chlamydial) in asymptomatic males and DNA amplification testing of urine for detection of chlamydial DNA have been used (6).

The current CDC-recommended therapy for NGU is azithromycin 1 g orally in a single dose or doxycycline 100 mg twice a day for 7 days (54). Alternative treatment includes erythromycin base 500 mg orally four times a day for 7 days, erythromycin ethylsuccinate 800 mg four times a day for 7 days, or ofloxacin 300 mg twice a day for 7 days. In patients who cannot tolerate the high dose of erythromycin, the dose can be halved and the duration of therapy extended to 14 days. Table 5.4 provides the 1998 CDC treatment recommendations for chlamydial infection of the lower genital tract. Doxycycline and azithromycin are similar in efficacy and toxicity (54). The major advantage of doxycycline is low cost, whereas azithromycin has the advantage of single-dose administration.

Recommended regimen
Azithromycin 1 g p.o. in a single dose
or
Doxycycline 100 mg p.o. two times a day for 7 days
Alternate Regimen
Erythromycin base 500 mg p.o. four times a day for 7 days
or
Erythromycin ethylsuccinate 800 mg p.o. four times a day for 7 days
or
Ofloxacin 300 mg p.o two times a day for 7 days or
Levofloxacin 500 mg orally for 7 days

TABLE 5.4. CENTERS FOR DISEASE CONTROL 2001 RECOMMENDED TREATMENT FOR CHLAMYDIAL INFECTION OF THE LOWER GENITAL TRACT

Routine treatment of female sex partners of men with NGU is indicated. One third of women whose male partners have NGU will have a chlamydial infection of the cervix; more than two thirds of those whose male partners with NGU are chlamydia positive will have such infections.

Epididymitis

A major role for *C. trachomatis* causing epididymitis in men younger than 35 years was suggested initially by Berger et al. (51), who isolated *C. trachomatis* from epididymal aspirates in five of six men with acute epididymitis. Stamm and coworkers (111) estimated that epididymitis complicates urethral chlamydial infections in 1% to 3% of cases. It has been estimated that 50% of the estimated 500,000 cases of acute epididymitis that occur annually in the United States are due to *C. trachomatis* (6,8). In men older than 35 years, coliform organisms were the major cause of epididymitis.

Clinically, chlamydial epididymitis manifests with unilateral scrotal pain, swelling, tenderness, and fever in young men who often have concomitant chlamydial urethritis (6). In some instances, the urethritis may be asymptomatic and only identified by a Gram stain demonstrating urethral inflammation (6).

Prostatitis

A link between chlamydial infection and prostatitis has not been established definitely (6). Paavonen et al. (121) estimated that prostatitis accompanies NGU in up to 20% of cases. Mardh and coworkers (120) suggested that *C. trachomatis* is associated with acute rather than chromic prostatitis. However, Bruce et al. (119) recovered *C. trachomatis* from early-morning urine specimens and/or prostatic fluid or semen in 56% of 70 patients with chronic prostatitis. Using transrectal biopsies of the prostate in men with proven chlamydial urethral infection and a tender prostate on digital palpation, Poletti (122) recovered *C. trachomatis* from 10 (33%) of 30 prostatic specimens.

Proctitis

Proctitis presents with anorectal pain, tenesmus, and rectal discharge. *Chlamydia trachomatis* has been associated with proctitis in both men and women (6,8,116). Quinn et al. (123) demonstrated that non-LGV immunotypes of *C. trachomatis* were associated with mild proctitis, with or without symptoms, in male homosexual populations.

Reiter Syndrome

Reiter syndrome develops in 1% to 2% of men following bouts of NGU (8). Genital chlamydial infection has been documented in approximately 50% of men with sexually acquired Reiter syndrome (118,124,125 and 126). Keat (118) noted that SARA also develops in men with NGU. Symptoms of Reiter syndrome appear 1 to 4 weeks after the onset of urethritis (8). The arthritis typically is asymmetric, involving the large joints of the lower extremities or the sacroiliac joints (8). The full syndrome also involves the eyes, skin, and mucous membranes. Manifestations of eye disease range from a transient, mild conjunctivitis to severe uveitis. Skin findings include keratoderma of the palms and soles and balanitis of the penis. Lesions involving mucous membranes are small ulcers of the palate, tongue, and oral mucosa. Even in the absence of treatment, these signs and symptoms regress but recurrences are common (8). When arthritis and/or Achilles tendon and plantar fasciitis are the only manifestations, the term sexually acquired reactive arthritis (SARA) has been used (118). *Chlamydia trachomatis* has been recovered from the urethra in one third of SARA cases and up to two thirds of cases having serologic evidence of previous chlamydial infection (8). The association of *C. trachomatis* infection and SARA has been strengthened by the use of direct immunofluorescence (127) and PCR (128) to detect *C. trachomatis* in joints of patients with reactive arthritis.

Schachter (8) has suggested that *C. trachomatis* infection may be a trigger antigen for Reiter syndrome resulting in an enhanced immune response in susceptible persons. Reiter syndrome and SARA seem to occur in a genetically predisposed population, with two thirds of patients having the histocompatibility antigen HLA-B27.

Chlamydial Genital Infection Of Women

In many ways, the clinical spectrum and epidemiology of *C. trachomatis* infection in women are similar to those associated with gonococcal infection (6,8,101). However, there also are major differences. Chlamydial infection generally is more frequent, often is asymptomatic, may be associated with nonspecific symptoms, or may exist in the absence of visible signs of infection. The diagnosis can be proven only by culture, use of antigen detection methods such as monoclonal antibody staining or immunoassay, or use of nucleic acid amplification tests such as PCR and LCR.

Despite the absence of clinically apparent disease, women infected with *C. trachomatis* may harbor the organism for long periods of time. The incubation period for *C. trachomatis* probably is 6 to 14 days, which is considerably longer than that for *N. gonorrhoeae.* As a result of the longer incubation period, the high rate of asymptomatic infection, and the persistent carrier state, a large reservoir of *C. trachomatis* infection exists in the population. This reservoir in the lower genital tract places women at risk for ascending infection to the upper genital tract with its resultant adverse effect on future reproductive health.

Bartholinitis

Chlamydia trachomatis produces an exudative infection of Bartholin's ducts similar to that seen with *N. gonorrhoeae* (6). Davies and coworkers (129) recovered *C. trachomatis* from Bartholin duct exudates in nine of 30 patients. Concurrent infections with gonococci were present in seven of these patients. At present, the

proportion of cases of bartholinitis regarded as chlamydial is not known.

Endocervicitis

The anatomic site within the female genital tract most commonly infected with *C. trachomatis* is the cervix. *Chlamydia trachomatis* is a major cause of MPC (130,131). However, it is clear that asymptomatic cervical infections with chlamydia also occur. Although approximately two thirds of women with chlamydial infection of the cervix do not have any signs or symptoms of infection, one third do have clinical evidence of infection (6,8,71,132). *Chlamydia trachomatis* does not cause vaginitis, as it will not grow in vaginal squamous epithelial cells. The organism seems to be a specific parasite of squamocolumnar cells; thus it only grows within the transitional zone and the endocervix. It is not associated with ectocervicitis. The infected cervix may range from a clinically normal result on examination to a severely eroded cervix with hypertrophic cervical erosion and a mucopurulent endocervical discharge. Dunlop and coworkers (133) were the first to describe follicle-like lesions (similar to those seen in the conjunctivae) that occur in the cervix in association with chlamydial infection. They described this finding of follicular cervicitis in 90% of mothers whose babies had chlamydial inclusion conjunctivitis of the newborn. Rees and coworkers (134) used colposcopy to evaluate the sexual partners of men with NGU. Of the women with endocervical cultures positive for *C. trachomatis,* more than 80% had hypertrophic cervicitis with mucopurulent endocervical discharge. Hypertrophic cervicitis is the term applied to the presence of cervical ectopy that is edematous, congested, and friable. Paavonen et al. (130) confirmed this association between mucopurulent endocervicitis and isolation of *C. trachomatis* from the endocervix.

Diagnosis of MPC is suggested by demonstrating (i) yellow or green mucopus on a swab of endocervical secretions (“positive swab test”); (ii) more than 10 PMNs per oil immersion field of a Gram stain of the endocervix; or (iii) friability, erythema, or edema within a zone of cervical ectopy (6,8,130,131). Brunham et al. (131) have suggested that MPC is the female counterpart of NGU in the male. A cutoff of $^{3}30$ PMNs per 1,000× field in Gram-stained smears of cervical mucus has been suggested to best correlate with chlamydial cervicitis (6).

Hobson et al. (135) demonstrated that women with clinical signs of chlamydial cervicitis, such as mucopurulent discharge or hypertrophic ectopy, yield greater numbers of chlamydial inclusion-forming units than those in whom chlamydial infection is not associated with signs and symptoms of cervicitis. Harrison et al. (132) noted that the prevalence of chlamydial infection was greater in women with cervical ectopy than in those without. Cervical ectopy is present in 60% to 80% of sexually active female adolescents, which is a much higher prevalence than that seen in women in their 30s and 40s (6). Possibly ectopy predisposes to chlamydial infection by providing exposure of more susceptible columnar epithelial cells to *C. trachomatis* at the time of exposure (6). This relationship may explain in part the high prevalence of chlamydia cervical infection among adolescents. Similarly, oral contraceptives are associated with ectopy, and this relationship may explain the increased risk for *C. trachomatis* infection of the cervix among users of oral contraceptives (6,63,132).

The complex microflora of the lower genital tract makes it difficult to delineate a single pathogen as the putative agent in cervicitis. However, data generally indicate that *C. trachomatis* is a major etiologic agent in mucopurulent endocervicitis. Rees and colleagues (134) noted that only two organisms, *C. trachomatis* and *N.*

gonorrhoeae, are found to be associated with chronic cervicitis and purulent endocervical discharge. Paavonen et al. (130) reported that *C. trachomatis* was recovered from the cervix with greater frequency in women with signs of cervicitis than in those without such signs. Paavonen (136) also noted that severe inflammatory atypia and/or dyskaryotic changes in Papanicolaou (Pap) smears occurred significantly more frequently in chlamydia-positive than in chlamydia-negative women. Mardh and coworkers (137) have suggested that this chlamydia-associated atypia represents a reparative atypia related to an infectious process. Paavonen et al. (138) obtained cervical biopsy specimens during colposcopy from patients with *C. trachomatis* isolated from the cervix. Severe inflammatory changes were noted in 45% of cases. The inflammation was characterized by heavy leukocytic and lymphocytic infiltration, intraepithelial microabscesses, and epithelial necrosis and ulceration (138).

Various studies have questioned the accuracy of using MPC as a predictor of chlamydial infection. Brunham et al. (131) noted in a symptomatic high-risk group of women for chlamydial infection (22% prevalence rate) a sensitivity of 59%, specificity of 86%, and positive predictive value of 54% for yellow mucopurulent discharge. Mosciki and coworkers (139) demonstrated in an adolescent nonpregnant population (18% prevalence rate) that mucopus had a sensitivity of 32%, specificity of 80%, and predictive value of 32% for predicting chlamydial infection. Similarly, Thejls et al. (140) and Nugent and Hillier (70) reported poor sensitivity, specificity, and positive predictive value with mucopus (swab test) for detection of chlamydial cervicitis (Table 5.5). These authors concluded that MPC is not a useful screening method for identifying women with chlamydial infection. Of concern is that in a general population of asymptomatic women with a prevalence rate of 3% to 5% for *C. trachomatis,* the positive predictive value would be even worse. In most of those studies, the presence of PMNs was a better predictor of chlamydial infection than was mucopus (70,131,139). It seems justified for the clinician lacking availability of chlamydial cultures, antigen detection methods, or nucleic acid amplification tests to consider managing cervicitis in the same manner that NGU in the male is managed. Thus, the physician would test for other pathogens, such as *N. gonorrhoeae* and, if none are found, treat empirically with azithromycin or doxycycline for a suspected chlamydial infection. The recommended regimen is azithromycin 1 g orally as a single dose or doxycycline 100 mg twice a day for 7 days (Table 5.4). Erythromycin in similar dosages would be indicated for pregnant women or those unable to tolerate tetracycline.

	Rate of Chlamydia Infection	Sensitivity	Specificity	Positive Predictive Value
Mucopus				
Brunham et al. [131][a]	22%	59%	86%	54%
Mosciki et al. [139][b]	18%	32%	80%	32%
Thejls et al. [140][c]	13%	26%	86%	31%
Nugent and Hillier [70][d]	14%	24%	89%	28%
Polymorphonuclear leukocytes				
Brunham et al. [131][a]				
≥10	22%	85%	83%	61%
Mosciki et al. [139][b]				
>5	18%	91%	85%	36%
Nugent and Hillier [70][d]				
>10	14%	58%	53%	18%
>30	14%	25%	86%	24%

[a]Cervical swab test.
[b]Symptomatic patients.
[c]Adolescents.
[d]Pregnant women.

TABLE 5.5. SENSITIVITY, SPECIFICITY, AND POSITIVE PREDICTIVE VALUE OF

MUCOPUS[a] AND POLYMORPHONUCLEAR LEUKOCYTES FOR CHLAMYDIAL INFECTION

It seems apparent that cervical infection with *C. trachomatis* is a major reservoir for the male and neonatal infections associated with this agent. In addition, the cervix is the source for major complications involving the upper genital tract, such as acute salpingitis. Thus, it is imperative that efforts be made to identify those women who are symptomatic and asymptomatic carriers of *C. trachomatis* in the cervix. As noted earlier, the prevalence of *C. trachomatis* infection (4,55,56 and 57) and the incidence of acute PID have been reduced significantly in geographic areas where intensive chlamydia control programs have been implemented (141).

Acute Urethral Syndrome

The acute urethral syndrome, which is defined as acute dysuria and frequent urination in women with pyuria but whose voided urine is sterile or contains fewer than 10^5 microorganisms per milliliter is a common and perplexing problem for the clinician. Paavonen (142) noted that 25% of women whose male partners had chlamydial urethritis had chlamydial infection in their urethra. Based on studies in STD clinics of women cultured for *C. trachomatis* from the cervix and urethra, 25% of positive women harbor the organism only in the urethra (63,142); an additional 50% harbor the organism in both the cervix and urethra.

Stamm and coworkers (143) identified a causative role for *C. trachomatis* in up to 25% of women presenting with the acute urethral syndrome. These investigators were able to show that *C. trachomatis* infection was present in ten of the 16 patients with the urethral syndrome, sterile bladder urine, and pyuria. Among the 32 patients with the urethral syndrome and sterile bladder urine, evidence of recent infection with *C. trachomatis* was demonstrated in ten of 16 with pyuria; only one of 16 without pyuria had such evidence. On the other hand, *C. trachomatis* was unlikely to be recovered from women with acute cystitis or women with the urethral syndrome and bladder bacteriuria.

The clinician must be aware that *C. trachomatis* will not be recovered from the urine, but that culture attempts must be performed via urethral swabs. Several findings on history are suggestive of *C. trachomatis* being the causative agent in women presenting with symptoms of acute urethral syndrome (143). These factors include a recent change in sexual partner, the use of oral contraceptives, and a longer duration of presenting symptoms (approximately 7 to 10 days) compared with women with acute cystitis or bacteriuria who present within 4 days. In addition, women with chlamydia are less likely to give a history of recurrent urinary tract infections, which is in contradistinction to women with acute cystitis or bladder bacteriuria. Although some women with chlamydial infection develop symptoms, the majority of women so infected are asymptomatic (6).

Stamm and colleagues (144) showed that antimicrobial therapy of the acute urethral syndrome using an agent effective against *C. trachomatis* was significantly more effective than placebo in eradicating urinary symptoms, pyuria, and the infecting

microorganism in women with the urethral syndrome due to coliforms, staphylococci, or *C. trachomatis.* In contradistinction, women with acute urethral syndrome and no pyuria did not benefit from antibiotic therapy.

Nonpuerperal Endometritis

Various investigations have suggested that endometritis in nonpregnant women is another manifestation of genital chlamydial infection (104,137,145,146 and 147). Histologic endometritis based on the presence of plasma cells and infiltration of the superficial epithelium by PMNs has been detected in nearly one half of patients with chlamydial MPC (6,108,109 and 110,148). The presence of histologic endometritis has been associated with both culture and immunohistologic detection of *C. trachomatis* (109,110). In addition, histologic endometritis can be detected in nearly all patients with chlamydial salpingitis (6).

As discussed in Chapter 14, histologic endometritis has been demonstrated with *N. gonorrhoeae* and the mixed anaerobic-aerobic bacteria associated with bacterial vaginosis. Mardh and coworkers (145) recovered *C. trachomatis* from the endometrium of three women with concomitant signs of salpingitis. These workers suggested that chlamydia ascends from the cervix, affects the uterine mucosa, and then spreads intracanalicularly from the endometrium to the fallopian tubes. Interestingly, they noted that the endometrial cultures could be positive despite negative cervical cultures. Mardh et al. (137) also reported that *C. trachomatis* was recovered from the endometrial aspirates from nine of 18 patients with laparoscopically confirmed PID. Endometrial biopsy specimens in women in whom *C. trachomatis* was isolated demonstrated heavy infiltration of monocytes. Similarly, Paavonen (147) confirmed the presence of histologic endometritis (based on the presence of five plasma cells per high-power field) in 47% of women with chlamydial endocervicitis. Wasserheit et al. (109) and Kiviat et al. (110) demonstrated the presence of *C. trachomatis* in association with histologic endometritis in women with laparoscopically confirmed acute salpingitis. Sweet et al. (108) also recovered *C. trachomatis* from the endometrial cavity of women with signs and symptoms of acute salpingitis. In their report, *C. trachomatis* was recovered from the endometrial cavity in 17 (24%) of 71 patients with acute salpingitis. Despite prompt clinical response to antibiotic therapy, 13 women treated with b-lactam antibiotics still had positive endometrial cultures for *C. trachomatis* at posttherapy evaluation. This suggests the presence of a subclinical, persistent chlamydial endometritis among patients with resolving acute PID. Jones et al. (149) reported that *C. trachomatis* was isolated from the endometrium in 12 (41%) of 29 women with cervical chlamydial infection. This finding suggests that there may be a large reservoir of women with chlamydial infection of their upper genital tract. Taken together, these studies demonstrate that endometritis is an important component of PID and an intermediate step in the spread of microorganisms from the cervix and/or vagina to the fallopian tubes.

The abnormal uterine bleeding (menorrhagia and metrorrhagia) often seen in patients with acute PID probably is due to the presence of concomitant endometritis (6). The role of persistent *C. trachomatis*, production of heat shock proteins (hsps), and initiation of the cell-mediated immune response leading to damage of the fallopian tube is discussed in detail in Chapter 14. Clearly, such a mechanism may explain a proportion of tubal factor infertility cases in which no history of an acute episode of PID exists.

Acute Salpingitis

The most serious complication of chlamydial infection in women is acute salpingitis (i.e., PID). The role of *C. trachomatis* as a pathogen in this disease has received considerable attention. Interestingly, the association of chlamydial infection of the female genital tract (as determined by giving birth to an infant who developed inclusion conjunctivitis of the newborn) and PID in the postpartum patient initially was recognized by ophthalmologists in the 1930s (150,151).

As reviewed by Cates et al. (152) and Sweet (153), microbiologic and serologic studies firmly established *C. trachomatis* as an important sexually transmitted organism that leads to acute PID. Cates and Wasserheit (1) suggested that the wide variation in reported rate of *C. trachomatis* recovery from patients with symptoms of PID was due to (i) differences among the populations studied; (ii) time period when the study occurred; (iii) methods used to recover microorganisms; and (iv) severity of infection (1). Table 5.6 summarizes various studies that detected *C. trachomatis* in patients with acute PID.

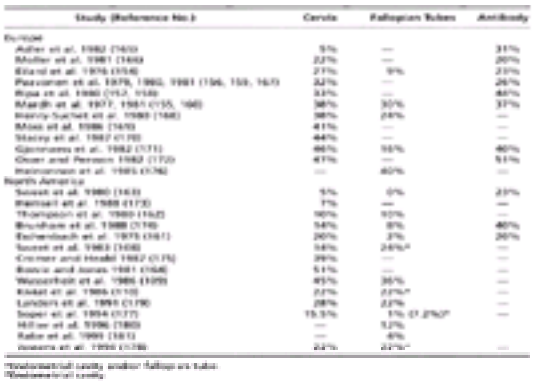


TABLE 5.6. SELECTED STUDIES FOR DETECTION OF *CHLAMYDIA TRACHOMATIS* IN WOMEN WITH ACUTE PELVIC INFLAMMATORY DISEASE

Initial evidence that *C. trachomatis* is an important etiologic agent in acute salpingitis came from European investigations (predominantly Scandinavian) (154,155,156,157,158,159 and 160). The first direct evidence of an association with *C. trachomatis* in acute salpingitis was documented by Eilard and colleagues (154), who isolated *C. trachomatis* from tubal specimens in two of 22 women with acute salpingitis undergoing laparoscopy. Of major importance was the report by Mardh et al. (155) of 30% isolation of *C. trachomatis* from the fallopian tubes of women with acute salpingitis in whom isolation attempts were performed on material aspirated from the involved fallopian tubes visualized by laparoscopy.

The rate at which this disease occurs differs in various geographic locales. Scandinavian investigations suggested that approximately half of acute salpingitis cases occurring in that area were due to *C. trachomatis* (154,155,156,157,158,159

and 160). Initial results in North America are not as clear-cut (161,162 and 163).

In addition to the isolation studies previously noted, a number of investigations have indirectly associated acute salpingitis with chlamydial infection. In Scandinavia, serologic studies have indicated that *C. trachomatis* is a frequent causative agent in acute salpingitis (156,157,158,159 and 160). These studies demonstrated that 19% to 80% of acute salpingitis patients had antichlamydial antibody present (156,157,158,159 and 160). Moreover, Paavonen et al. (156,159) in Finland demonstrated that 19% to 26% of patients with acute salpingitis had a fourfold increase in chlamydial antibody. Treharne et al. (157) and Mardh et al. (160) demonstrated that antibody titers were correlated with the severity of clinically graded tubal inflammation seen at the time of laparoscopy. Taken together, these studies from Scandinavia suggest that in the 1970s and 1980s, the major etiologic agent for acute salpingitis in that geographic area was *C. trachomatis*. This was a dramatic change in the etiologic pattern from that of the previous decades. In the mid-1960s, almost 50% of acute salpingitis cases in this area had gonorrhea, whereas by the 1980s, less than 10% of all salpingitis cases were infected with *N. gonorrhoeae.* Based on culture data (30%) and serologic data, between 30% and 67% of acute salpingitis cases now are associated with chlamydia as the etiologic agent in Scandinavia.

Until the mid-1980s in the United States, evidence suggested that chlamydia-associated acute salpingitis occurred much less frequently than what was reported from Scandinavia (161,162 and 163). These initial studies noted recovery of *C. trachomatis* from the fallopian tube or cul-de-sac aspirate in 0% to 10% of patients with acute salpingitis (161,162 and 163). Sweet and coworkers (163) did not isolate a single *C. trachomatis* from the fallopian tube exudate of 37 women undergoing laparoscopic evaluation with a confirmed diagnosis of acute salpingitis. Eschenbach and colleagues (161) recovered chlamydia from one of 102 patients. Thompson and coworkers (162) were able to recover chlamydia from intraperitoneal sites from three of 30 patients with acute salpingitis; however, two of their three isolates were from the cul-de-sac fluid, and it is uncertain whether this reflected vaginal contamination or true intraperitoneal infection. Indirect evidence for *C. trachomatis* as a causative agent for acute salpingitis in the United States did, however, exist. Cervical isolation rates in patients diagnosed with acute salpingitis ranged from 5% to 20% (161,162 and 163). In Canada, Bowie and Jones (164) presented evidence supporting a major etiologic role for *C. trachomatis* in acute salpingitis in North America. They reported that *C. trachomatis* was recovered from the cervix of 50% of women in an STD clinic diagnosed as having PID, compared with 20% of women attending the STD clinic who did not have acute salpingitis. In summary, studies from Scandinavia demonstrated a twofold increased cervical isolation rate of *C. trachomatis* and a 20-fold increased fallopian tube isolation rate compared with initial U.S. studies. Despite apparent differences in these recovery rates, the serologic evidence for an association between chlamydia and PID was quite similar. In the United States, serologic evidence for chlamydial infection in patients with acute salpingitis was noted in 20% to 23% (161,163).

Several factors were postulated to explain these differences between Swedish and U.S. isolation rates. First, there were significant differences in the methods of specimen collection. Swedish investigations used needle aspiration and/or needle biopsy of the fimbria at the time of laparoscopy. In the United States, culture attempts were made on purulent tubal exudates. Because *C. trachomatis* is an

intracellular organism, successful isolation may require the presence of fresh infected cells in the inoculum. A second reason is that the patient groups that were studied in the United States and Sweden were not comparable. In the United States, investigations using intraperitoneal cultures were based on hospitalized patients who in general presented to the emergency room with acute disease characterized by high fever and peritonitis. Swedish investigators evaluated all patients with acute salpingitis, including many with clinically mild disease (often afebrile), who would not have been diagnosed as such in the United States where more rigid diagnostic criteria (i.e., fever, leukocytosis) were applied in the diagnosis of acute PID. Svensson et al. (182) noted that patients presenting with acute salpingitis and *C. trachomatis* tended to have milder clinical disease, were less often febrile, and had mild symptoms for longer periods of time than women admitted with gonococcal or nongonococcal-nonchlamydial salpingitis. Paradoxically, the women documented as having chlamydial salpingitis in Svensson's group had the highest erythrocyte sedimentation rates and the more severe inflammatory changes noted at the time of laparoscopy (182).

In the mid-1980s in the United States, studies that used appropriate methodology for obtaining chlamydial specimens (i.e., tubal biopsy, tubal aspirate, swab of endosalpinx, endometrial biopsy, and/or protected endometrial aspirate) confirmed that *C. trachomatis* was a major etiologic agent for acute PID (108,109 and 110). Sweet and coworkers (108) reported recovery of *C. trachomatis* from the upper genital tract in 17 (24%) of 71 patients with acute salpingitis. Wasserheit et al. (109) confirmed that *C. trachomatis* was a major cause of PID in the United States. They reported that 14 (61%) of 23 women with salpingitis and/or plasma cell endometritis had *C. trachomatis* identified in the upper genital tracts. Kiviat et al. (110) similarly confirmed the major role played by *C. trachomatis* in the etiology of acute PID. They demonstrated the presence of the organism in the cervix of 22% and the fallopian tube and/or endometrial cavity of 22% of women with laparoscopically confirmed acute PID. Jossens et al. (178) reported recovery of *C. trachomatis* from 22% of 548 women with clinical PID. In contradistinction, Soper et al. (177) recovered *C. trachomatis* from the peritoneal cavity in only 1.2% of 89 laparoscopy confirmed cases of acute PID, although the organism was present in the endometrium of 7.2%. In their study, *N. gonorrhoeae* was the predominant organism recovered from 73% of acute PID patients. Rees (183) provided additional data supporting the role of *C. trachomatis* in acute PID. In a large group (n = 343) of women randomly treated for gonorrhea with either penicillin or tetracycline, a significantly greater proportion of those who received penicillin subsequently developed salpingitis; in many of these cases, *C. trachomatis* persisted in the cervix (183). It is estimated that *C. trachomatis* currently is responsible for 20% to 40% of clinically apparent acute PID cases in the United States (1,5,153).

Cates and Wasserheit (1) have estimated that clinically apparent PID (symptomatic or visually confirmed) accounts for less than half of the total cases of PID. The remaining cases are due to unrecognized (“silent” or “atypical”) PID (23). Thus, chronic, subacute, or latent upper genital tract infection is present in a large number of women (23). Both the magnitude and an accepted definition of these unrecognized infections have not been established. Unfortunately, unrecognized PID appears as likely as clinically apparent PID to result in progressive scarring of the fallopian tubes leading to tubal factor infertility and ectopic pregnancy (184). *Chlamydia trachomatis* appears to be associated with these milder or unrecognized presentations of acute

PID (182).

The ability of *C. trachomatis* to produce acute salpingitis has been documented further in several animal models. Ripa et al. (185) and Moller et al. (186) demonstrated that *C. trachomatis* can cause acute salpingitis when it reaches the fallopian tubes of grivet monkeys. Moller et al. (187) demonstrated that the histologic findings in the fallopian tubes of patients with acute salpingitis due to *C. trachomatis* were similar to those previously described for gonococcal salpingitis and to those seen in the grivet monkey experimentally infected with *C. trachomatis.* Multiple elegant studies by Patton and coworkers (188,189,190 and 191) in the pig-tailed macaque confirmed the putative role *C. trachomatis* in the etiology and pathogenesis of acute salpingitis, especially the importance of repeated chlamydial infections in producing tubal scarring.

Numerous studies using rodent models and nonhuman chlamydia strains similarly demonstrated the ability of chlamydia to cause acute salpingitis, tubal screening, and infertility (192,193,194,195 and 196). Swenson et al. (192), using the mouse pneumonia biovar of *C. trachomatis*, reported that inoculation of chlamydia into the ovarian bursa of mice resulted in acute salpingitis. Inclusions were seen in histologic sections, and the organism could be recovered from infected tissues for up to 21 days. Although the inflammatory response decreased after 21 days, gross hydrosalpinges had developed in animals examined between 23 and 48 days after inoculation. Interestingly, Gibson and coworkers (197) described similar findings in humans and reported that women with tubal factor infertility and antichlamydial antibodies were significantly more likely to have hydrosalpinx than infertility patients without chlamydial antibodies. In a subsequent investigation, Swenson and Schachter (193) demonstrated that chlamydial infection of the upper reproductive tract of mice prior to mating resulted in infertility. This adverse effect on fertility produced by chlamydial infection occurred long after apparent resolution of the acute infection. Additional animal model work using the guinea pig inclusion conjunctivitis agent, which is a *C. psittaci* strain, produced acute salpingitis (194,195 and 196).

Further support for the role of *C. trachomatis* in the etiology and pathogenesis of acute PID arises from a large number of studies demonstrating a statistically significant association of tubal factor infertility (198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221 and 222) and ectopic pregnancy (223,224,225,226,227,228,229 and 230) with previous systemic chlamydial infection identified by the presence of antibody against *C. trachomatis*. These findings are discussed in the section on Sequelae of Pelvic Inflammatory Disease.

PATHOGENESIS OF CHLAMYDIAL INFECTION

Several interesting pieces of evidence support a role for the host defense system via cell-mediated immunity in the development of long-term sequelae secondary to chlamydial infection. Multiple investigations have provided data suggesting that chlamydial PID is a cell-mediated immune disease probably resulting from immune responses to chlamydial heat shock protein 60 (Hsp 60) (191,231,232,233,234,235,236,237,238,239,240,241,242,243,244 and 245). It has been hypothesized that this inflammatory immune response is similar to a delayed hypersensitivity reaction that results in damage to the fallopian tube (231,232,233,234,235,236 and 237,245). Such a response is similar to the

mechanism by which *C. trachomatis* produces scarring and blindness in ocular trachoma (246).

As reviewed by Ward (247), persistent and repeated chlamydial infections are particularly associated with pathologic disease (247). Interferon gamma (IFN-g) plays a major role in the immune response to chlamydia and the subsequent inflammatory process (247). Interferon gamma is a critical factor for induction of delayed chlamydial development and thus restricting chlamydial infection. However, delayed development results in persistent expression of chlamydial hsps, which not only share antigens with other bacterial hsps but with human hsp (247). The damage and scarring associated with chlamydial infection appear to be dependent on four mechanisms of chlamydial disease: (i) persistent chlamydial infection; (ii) role of cytokines in chlamydial infection; (iii) role of chlamydial hsps in the pathogenesis of disease; and (iv) host genotype (247).

Whereas the normal chlamydial development cycle is a productive cycle of infection resulting in release of infectious elementary bodies, persistent chlamydial infection is associated with incomplete chlamydial development with sporadic release of elementary bodies (247). This incomplete growth cycle may be induced by either inappropriate antibiotic treatment (e.g., penicillin) or cell-mediated immune response (e.g., IFN-g as discussed earlier). Such persistent ("latent") infection can revert over to infection and disease (247).

The hallmark of chlamydial infection is an inflammatory process that is exacerbated by reinfection and subsequently results in tissue damage and scarring (245,247). Interaction of *C. trachomatis* with the cytokine network is a key element in disease production. Chlamydial infection produces a cytokine response by (i) direct infection of epithelial cells (248); and (ii) interaction with cells of the immune system (249). Rasmussen et al. (248) demonstrated that infection of cervical epithelial cells with *C. trachomatis* induced production of the proinflammatory cytokines interleukin-8, GRD-g, granulocyte-macrophage colony-stimulating factor, and interleukin-6 (248). Unlike other invasive bacteria that induce a rapid and transient cytokine response, chlamydia induces an epithelial cytokine response that is delayed until 20 to 24 hours after infection, persists throughout the chlamydial growth cycle, and requires bacterial protein synthesis. Rasmussen et al. (248) concluded that the acute host response to *Chlamydia* at the mucosal surface might primarily be initiated and sustained by epithelial cells, which are the target for chlamydial infection. Response to chlamydial infection by the cells of the immune system is a Th1-like response, with production of interleukin-2 and IFN-g (247). This Th1 response is crucial to resolving established chlamydial infection. However, as discussed earlier, it also can result in persistent chlamydial infection and its associated adverse complications.

Heat shock proteins are a family of closely related proteins that are widely distributed in virtually all organisms and expressed when organisms are exposed to stress (231,245,247,250). The major chlamydial hsps (12, 60, and 75 kd) are partially (40% to 50%) homologous with human mitochondrial proteins Hsp 10, Hsp 60, and Hsp 70 (247). Thus, the concept has evolved that immune responses to chlamydial hsps, particularly Hsp 60, initiates (by antigenic mimicry) an autoimmune response against related human hsps (247). Central to this mechanism of pathogenesis is IFN-g (245,247,250). Beatty and coworkers (251) demonstrated that although treatment of chlamydial-infected cells with IFN-g inhibited chlamydial development, it permitted expression of Hsp 60. As an extension of this finding, it appears that in chronically or

acutely infected persons, continued chlamydial Hsp 60 expression (secondary to action of IFN-g) initiates the chronic inflammatory responses associated with fibrosis and scarring characteristic of the sequelae of chlamydial infection (e.g., blinding trachoma, PID, infertility, and ectopic pregnancy) (247). In humans, a number of studies have demonstrated an association between antibody to chlamydial Hsps and the chronic sequelae of chlamydial infection, such as PID, infertility, ectopic pregnancy, and perihepatitis (236,237,238,239,240,241,242 and 243). Wager et al. (238) and Brunham et al. (239) demonstrated that *C. trachomatis* seropositive women with ectopic pregnancy had antibodies to a Triton X-extractable 57-kd protein antigen of *C. trachomatis*. Wager et al. (238) documented that this protein antigen was a *C. trachomatis* Hsp 60 homologue. Witkin et al. (232), Peeling et al. (236), Eckert et al. (237), and Domeika et al. (243) showed a significant association between the presence of antibodies to chlamydial Hsp 60 and PID. Similarly, Toye et al. (240), Arno et al. (241) and Witkin et al. (244) noted an association of antibodies to chlamydial Hsp 60 and tubal factor infertility. Money and coworkers (242) demonstrated that antibodies to chlamydial Hsp 60 were associated with laparoscopically verified perihepatitis. Thus, it appears that cell-mediated immune response to this antigen plays an important pathogenic role in *C. trachomatis*-associated sequelae to acute PID.

Host genotype appears to play an important role in determining the severity of human disease following chlamydial infection (247). Kimani et al. (252) studied 306 female sex workers in Nairobi, Kenya, 44 of whom developed chlamydial or combined chlamydial and gonococcal PID. These investigators noted that major histocompatibility complex Class I HLA-A31 was independently associated as a risk factor for PID (odds ratio [OR], 5.6; 95% confidence interval [CI], 1.1–29.4). Recently, Cohen and coworkers (253) demonstrated an association of specific HLA Class II alleles with *C. trachomatis* microimmunofluorescence seropositivity among women with tubal infertility. They noted that among infertile women, DQA*0101 and DQB*0501 alleles were positively associated with *C. trachomatis* tubal infertility (OR, 4.9; 95% CI, 1.3–18.6 and OR, 6.8; 95% CI, 1.6–29.2, respectively) (253). These authors postulated that the DQ locus might modify susceptibility to, and pathogenicity of, *C. trachomatis* infection (253).

Sequelae Of Pelvic Inflammatory Disease: Infertility and Ectopic Pregnancy

The long-term follow-up investigations of Westrom (254) demonstrated that women who had acute PID were at significantly increased risk to develop tubal factor infertility or ectopic pregnancy. The incidence of infertility in the United States reportedly is increasing (255,256). It is estimated that 15% to 30% of involuntary infertility is secondary to the consequences of acute PID (255). Similarly, the prevalence of ectopic pregnancy has increased dramatically, with a fourfold increase over the past 2 decades.

Following Westrom's landmark studies, subsequent investigations of PID and infertility focused on the role of *C. trachomatis* (Table 5.7). This singling out of chlamydia was due in part to the recognition of its role in acute PID, its ability to produce severe tubal inflammation with an associated poor prognosis for fertility, and the availability of serologic studies that could be used in case-control studies. However, these studies generally were accomplished before the recognition of *C. pneumonia* (TWAR) as a human pathogen and the cross-reactivity of this organism with *C. trachomatis*. Several of these studies also screened their population with

gonococcal antibodies and noted a pattern similar to that seen with *C. trachomatis,* where patients with tubal factor infertility had significantly greater rates of antigonococcal antibody seropositivity (208,209,221,222). Minassian and Wu (256a) demonstrated that, in addition to its value in screening for tubal factor infertility, serum antichlamydia antibody level is a useful tool for predicting the severity of tubal factor infertility. A variety of animal model studies also demonstrated the role of *C. trachomatis* in the pathogenesis of tubal infertility (193,257).

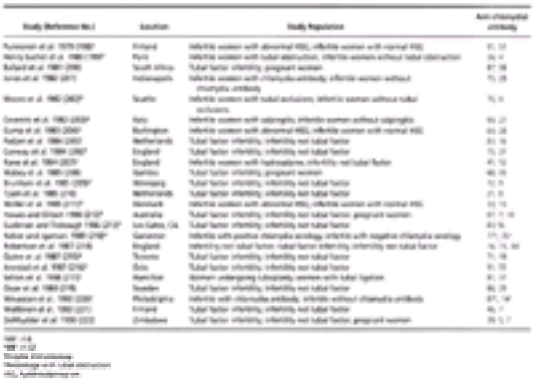


TABLE 5.7. STUDIES DEMONSTRATING AN ASSOCIATION BETWEEN *CHLAMYDIA TRACHOMATIS* INFECTION AND INFERTILITY

The association of *C. trachomatis* in the pathogenesis of tubal factor infertility initially was demonstrated by Punnonen et al. (198), who reported that 21 (91%) of 23 infertility patients with abnormal hysterosalpingograms had antibody titers against *C. trachomatis* versus 52 (50%) of 105 infertility patients with normal hysterosalpingograms and 20 (29%) of 68 pregnant controls. These investigators also noted that the mean geometric titer of antibody against *C. trachomatis* was significantly higher in infertility patients with abnormal hysterosalpingograms compared to those with normal hysterosalpingograms. Subsequently, a large number of retrospective case-control serologic studies in a wide variety of populations and geographic areas demonstrated an association of previous chlamydial infection with tubal factor infertility (Fig. 5.3) (198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221 and 222).

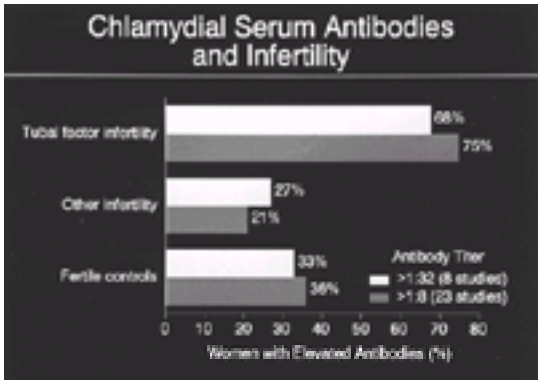


FIGURE 5.3. Summary of case-control serologic studies demonstrating an association of previous chlamydial infection with tubal factor infertility.

Henry-Souchet and coworkers (199) reported that chlamydia antibody was present in 32 (50%) of 64 infertility patients with tubal obstruction or pelvic adhesions compared with 20% of patients whose infertility was due to other factors. Moore et al. (202) noted that women with tubal factor infertility were strongly correlated with chlamydia seropositivity in contradistinction to infertility due to nontubal factors. Cevenini et al. (203) reported analogous findings in Italian women in whom chlamydial antibody was significantly higher in infertility patients with evidence of tubal disease than in women without. In Britain, Conway et al. (206), Kane et al. (207), and Robertson et al. (214) demonstrated a significant association between tubal factor infertility and chlamydial antibody, suggesting previous chlamydial infection. Canadian studies by Brunham et al. (209), Sellors et al. (217), and Quinn et al. (215) provided additional confirmation of the association between previous chlamydial infection and tubal factor infertility. Anestad et al. (216) reported that the prevalence of chlamydial antibody was significantly higher in Norwegian women with tubal factor infertility. Additional studies from Scandinavia reported similar findings (211,218,221). Dutch investigators provided further confirmation of this relationship (205,210). Ballard et al. (200), Mabey et al. (208), and DeMuylder et al. (222) demonstrated that women with tubal factor infertility in Africa had significantly higher rates of chlamydia seropositivity.

Of great concern, Gump et al. (204) noted that approximately half of the women with evidence of prior PID did not recall a past history of diagnosis of, or treatment for, acute PID. This finding, which was confirmed by Moore et al. (202), Jones et al. (201), and Sellors et al. (217), suggests that either mild cases of acute PID are not being diagnosed or that clinically silent chlamydial infection of the upper genital tract can result in significant tubal damage and subsequent obstruction. Taken together, these retrospective studies strongly suggest that chlamydial infection is a major cause of tubal factor infertility occurring subsequent to prior PID (198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221 and 222).

Despite the impressive seroepidemiologic data documenting an association between antibodies against *C. trachomatis* and tubal factor infertility, attempts to recover *C. trachomatis* from the fallopian tubes and/or cul-de-sac in these infertility patients has yielded inconsistent results. Henry-Souchet et al. (199,258) isolated *C. trachomatis*

from the tubes and/or peritoneum in 35% of infertile women with chromic tubal inflammation, 21% with no evidence of inflammation, and none of the controls. Sayed and coworkers (259) reported recovery of *C. trachomatis* from fallopian tube biopsies of five infertile women with cornual obstruction. On the other hand, Cevenini et al. (203) Moore et al. (202), Sellors et al. (217), and Anestad et al. (216) were unable to isolate *C. trachomatis.* However, these studies all used culture, and whether new technology such as DNA amplification would demonstrate the presence of chlamydia remains to be determined.

Conflicting results have been reported on the relationship between circulating antichlamydial immunoglobulin G (IgG) antibodies (evidence of prior systemic chlamydial infection) and *in vitro* fertilization (IVF) outcome (215,260,261,262,263,264,265 and 266). Rowland and coworkers (260) first demonstrated an association between prior chlamydial infection (elevated antichlamydial IgG levels) and poor IVF outcome, with prior chlamydial infection reducing pregnancy rates by 50%. Similarly, Lunenfeld et al. (261) reported a significant difference in the prevalence of antichlamydial IgG antibody between IVF term pregnancies and failures (abortion or nonconception) (47% vs. 73%, respectively; $p < 0.01$). Witkin and Ledger (262) noted that women with recurrent spontaneous abortions were significantly more likely to have elevated antichlamydial IgG antibody titers than fertile controls. These authors reported elevated IgG titers in 7 (41.1%) of 17 women with three prior abortions and 6 (60%) of 10 women with four prior abortions versus 20 (13.5%) of 148 fertile controls ($p = 0.01$ and $p = 0.006$, respectively) (262). In 145 women undergoing IVF, Licciardi et al.(263) demonstrated elevated levels of antichlamydial IgG antibodies in 20 (69%) of 28 spontaneous abortions compared to 9 (23.7%) of 38 ($p < 0.001$) successful pregnancies. However, studies by Quinn et al. (215), Torode et al. (264), Tasdemir et al. (265), and Sharara et al. (266) failed to confirm these results and could not detect an association between elevated antichlamydial IgG titers and poor IVF outcome.

Later investigations demonstrated an association of chlamydial infection and adverse IVF outcome (267,268). Witkin et al. (267) assessed the relationship among asymptomatic chlamydial infection, immune sensitization to hsp, and the ability of embryos to implant and develop following IVF (267). They noted that in women with term births, cervical immunoglobulin A (IgA) antibodies to chlamydial hsp were detected in 5 (7.3%) and IgA antibody to chlamydial structural components in 1 (1.5%). In contrast, among women whose embryo transfers did not result in an ongoing pregnancy, 36 (27.7%) had cervical IgA antibodies to chlamydial hsp and 24 (18.5%) had antichlamydial structural component IgA ($p = 0.0007$ and $p = 0.0002$, respectively) (267). In addition, positive results with PCR for *C. trachomatis* were present in 3 (4.4%) women with term births compared to 15 (11.5%) of the failures. These authors suggested that unsuspected *C. trachomatis* infection or reactivation of an immune response to the chlamydial hsp may induce an inflammatory reaction in the uterus that either impairs implantation and/or leads to immune rejection of *in vitro* fertilized embryos and uterine transfer (267). Witkin and coworkers (268) later provided additional evidence supporting a role for undetected *C. trachomatis* infection and adverse IVF outcome. These authors demonstrated a strong correlation between the presence of *C. trachomatis* detected by PCR (in the face of negative cultures) and failure to become pregnant and spontaneous abortion after embryo transfer. In this study, *C. trachomatis* was detected in 2 (1.8%) of 112 term pregnancies, 3 (27.3%) of 11 spontaneous abortions ($p = 0.004$), 1 (3.3%) of 30 with biochemical pregnancies, and 13 (9.6%) of 135 with pregnancy after embryo transfer

(p = 0.013).

The past 2 decades have shown a dramatic increase in the number of ectopic pregnancies (269). This phenomenon often has resulted from previous tubal infection. As noted by Westrom (254), women who had PID are at a 6- to 10-fold increased risk for ectopic pregnancy. Investigations also demonstrated an association between ectopic pregnancy and previous chlamydial infection (presence of antichlamydial IgG antibody) (Table 5.8 and Fig. 5.4) (204,221,222,223,224,225,226,227,228,229 and 230). Gump et al. (204) were the first to suggest an association between prior chlamydial infection and ectopics when they reported that women with antichlamydial antibodies followed prospectively after infertility evaluations had significantly more ectopic pregnancies (32%) than infertility patients without chlamydial antibodies (4%). In Sweden, Svensson et al. (223) reported that women with ectopic pregnancies had a significantly higher rate of antichlamydial antibody (65%) than pregnant controls (25%) or patients with nontubal factor infertility (11%). The postsalpingitis group (69%) with ectopic pregnancy had antichlamydial antibodies significantly more frequently than the nonpostsalpingitis group. As noted in the infertility studies, 46% of women with ectopic pregnancy had no history of PID but had postinflammatory adhesions of the contralateral tube (223). Brunham and coworkers (224) found a higher rate of antichlamydial antibody in women with ectopic pregnancies than in matched controls (56% vs. 22%). Hartsford et al. (225) demonstrated a significant association of prior chlamydial infection with ectopic pregnancy and the presence of contralateral tubal disease. Moreover, the mean geometric IgG titers for *C. trachomatis* were significantly higher in patients with contralateral chronic salpingitis (78.9 vs. 13.1) (225). Chow et al. (229) confirmed this association between ectopic pregnancy and previous *C. trachomatis* infection as evidenced by the presence of antichlamydial antibody. In a large, matched control study of nearly 300 ruptured ectopics, these investigators noted the presence of antichlamydial antibody (IgG 1:64) in 71% of ectopics compared with 39% of age- and race-matched controls at 12 to 24 weeks' gestation (229). Walters et al. (227) reported similar findings in the United States. In European reports, Robertson et al. (226) and Miettinen et al. (221) confirmed the association of ectopic pregnancy and previous chlamydial infection. Similarly, Chaim et al. (228) in Israel and DeMuylder et al. (222) in Africa found the same association. However, Phillips et al. (230) in Boston, Massachusetts, failed to confirm an association between ectopic pregnancy and previous chlamydial infection. Cumming et al. (269a) suggested that “silent” salpingitis may be related to ectopic pregnancy and that laparoscopy cannot exclude low-grade intraluminal infection in the fallopian tube. In their group of 27 ectopic pregnancies, 12 (44%) had undergone a laparoscopy at which “normal” tubal morphology had been noted. Eight of these tubes were available for histologic evaluation, and all eight had evidence of ongoing, low-grade salpingitis.

Study (Reference No.)	Location	Study Group	Chlamydial antibody (%)
Gung et al. 1989 [264]*	Burlington	Ectopic pregnancy vars. infertility patients seropositive; infertility patients seronegative	32, 4
Svensson et al. 1995 [223]*	Sweden	Ectopic pregnancy; intrauterine pregnancy; male factor infertility	65, 21, 11
Brunham et al. 1986 [224]*	Winnipeg	Ectopic pregnancy; pregnant women	56, 12
Hartford et al. [225]*	Los Angeles	Ectopic with disease in contralateral tube; ectopic with normal contralateral tube	50, 0
Robertson et al. 1988 [226]*	England	Ectopic pregnancy; intrauterine pregnancy	32, 4
Walters et al. 1988 [227]*	San Antonio	Ectopic pregnancy; intrauterine pregnancy	44, 20
Chaim et al. 1989 [228]*	Israel	Ectopic pregnancy; healthy women	32, 8
Miettinen et al. 1990 [217]*	Finland	Infertile women with ectopic; infertile women with normal tubes	40, 7
Chow et al. 1990 [229]*	Los Angeles/San Francisco	Ectopic pregnancy; intrauterine pregnancy	71, 19
DeMeyster et al. 1994 [222]*	Zimbabwe	Ectopic pregnancy with abnormal tube; ectopic and normal tubes; pregnant women	26, 5, 7
Phillips et al. 1992 [230]*	Boston	Ectopic pregnancy; intrauterine pregnancy	35, 20

[illegible]
[illegible]

TABLE 5.8. RELATIONSHIP OF PREVIOUS CHLAMYDIAL INFECTION AND ECTOPIC PREGNANCY

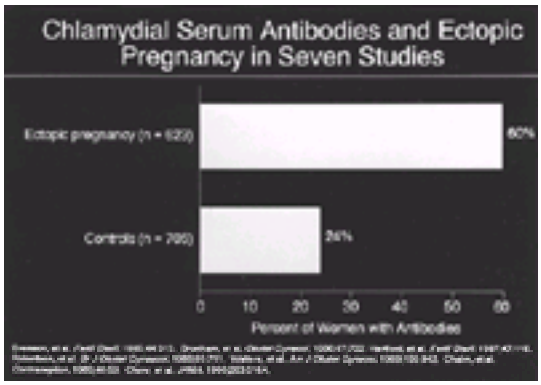


FIGURE 5.4. Association of ectopic pregnancy and previous chlamydial infection as determined by anti-chlamydial immunoglobulin G antibody.

It appears that the two major sequelae of acute PID, tubal factor infertility and ectopic pregnancy, have been strongly associated with previous chlamydial infection, as documented by the presence of antichlamydial antibody.

Fitz-Hugh and Curtis Syndrome

Acute perihepatitis is a localized fibrinous inflammation affecting the anterior surface of the liver and the adjacent parietal peritoneum. The sequelae are fibrous adhesions between the liver and the diaphragm (Fig. 5.5). When this condition occurs in association with acute salpingitis, it has been known as the Fitz-Hugh and Curtis (FHC) syndrome. It is important to recognize that the symptoms of salpingitis often are moderate or even absent in this syndrome. The clinical picture often is characterized by acute onset of severe right upper quadrant abdominal pain resembling that of acute cholecystitis. This syndrome was first described in 1919 by Stajano (270). Curtis (271) in 1930 and Fitz-Hugh (272) in 1934 related the syndrome to gonococcal infection. Until recently, FHC syndrome was primarily

believed to be a complication of gonococcal infection.

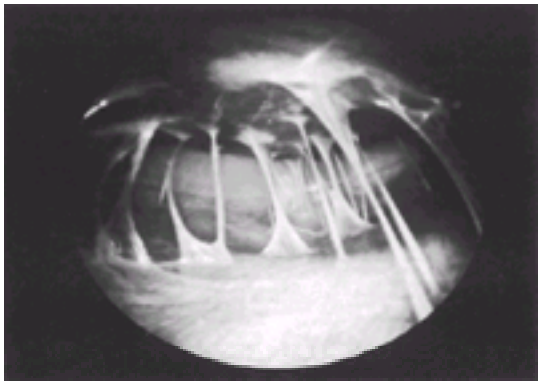


FIGURE 5.5. Laparoscopic view of Fitz-Hugh and Curtis syndrome.

Chlamydia trachomatis as a possible cause of FHC syndrome was first suggested by Muller-Schoop et al. (273). These investigators found serologic evidence of recent chlamydial infection in nine of 11 patients with both perihepatitis and peritonitis. Subsequent investigations confirmed the association between *C. trachomatis* and FHC syndrome (274,275,276,277,278,279 and 280). Wang et al. (277) reported that the geometric mean titer of chlamydia antibody was significantly higher in patients whose PID was complicated by perihepatitis compared with those with uncomplicated PID. Money et al. (280) demonstrated that antibodies to chlamydial Hsp 60 were associated with laparoscopically confirmed perihepatitis. Moller and Mardh (*personal communication*, 1993) described the presence of perihepatitis in a gravid monkey in which the tubes had been ligated and which had undergone experimental inoculation of *C. trachomatis.* Thus, an etiologic relationship between *C. trachomatis* and FHC syndrome seems evident. However, other organisms involved in acute salpingitis probably also are associated with FHC syndrome.

PERINATAL INFECTION WITH *CHLAMYDIA TRACHOMATIS*

Infection with *C. trachomatis* in pregnant women is a major concern. The prevalence of chlamydial infection of the cervix in pregnant women has been reported to range from 2% to 37%, with the general estimate for the United States being 5% (Table 5.9). In general, the higher prevalence rates occur in studies conducted among indigent patients in urban inner city areas and among adolescents (2). In addition, young unmarried women, a history of frequent past sexual activity, black ethnicity, and oral contraceptive usage are associated with an increased risk for cervical chlamydia during pregnancy.

Study (Reference No.)	City	Prevalence of Maternal Infection
Hammerschlag et al. 1979 (90)	Boston	2.0%
Schachter et al. 1986 (282)	San Francisco	4.7%
Sweet et al. 1987 (290)	San Francisco	4.5%
Schachter et al. 1978 (91)	San Francisco	5.0%
Cohen et al. 1990 (292)	Cleveland	5.75%
Harrison et al. 1983 (289)	Tucson	8.0%
Frommell et al. 1979 (92)	Seattle	8.8%
Gravett et al. 1986 (283)	Seattle	9.0%
Mardh et al. 1980 (287)	Lund	9.0%
Chandler et al. 1977 (93)	Seattle	12.1%
Fitzsimmons et al. 1986 (285)	Philadelphia	15.0%
Thompson et al. 1982 (288)	Atlanta	16.0%
Heggie et al. 1981 (94)	Cleveland	18.0%
Baselski et al. 1987 (286)	Memphis	21.0%
Ryan et al. 1990 (291)	Memphis	21.1%
Ismail et al. 1981 (284)	Chicago	21.3%
Martin et al. 1981 (95)	New Orleans	23.0%
Harrison et al. 1983 (281)	New Mexico	27.0%
Handy et al. 1984 (282)	Baltimore	37%

TABLE 5.9. PREVALENCE OF *CHLAMYDIA TRACHOMATIS* IN PREGNANT WOMEN IN THE UNITED STATES

Although it is well documented that infants born through an infected birth canal are likely to become infected with *C. trachomatis* and develop inclusion conjunctivitis and/or pneumonia, the effect of maternal chlamydial infection on pregnancy outcome and perinatal complications, such as preterm labor and delivery, PROM, and postpartum endometritis, remains less clear.

Infections Of The Neonate

The infant delivered vaginally to a woman with chlamydial infection of the cervix has a 60% to 70% risk to acquire the infection during passage through the birth canal (41,42,43 and 44,140). Approximately 20% to 50% of exposed infants will develop conjunctivitis in the first 2 weeks of life, and 10% to 20% of the infants will develop pneumonia within 3 to 4 months (Table 5.10). *In utero* transmission is not known to occur, and infants delivered by cesarean section are not at risk to acquire chlamydial infection unless there has been PROM. The determinant of whether chlamydial infections of the newborn represent a major medical problem in a specific population group is the prevalence rate of chlamydial infections of the cervix in that population. This carriage rate can vary broadly. The reported incidence has ranged from 2% to 37% (90,91,92,93,94 and 95,281,282,283,284,285,286,287,288,289,290,291,292 and 293), with the higher prevalence rates occurring in inner city and lower socioeconomic patient groups.

Study (Reference No.)	Conjunctivitis	Pneumonia
Alexander and Harrison (98)	9/18 (50%)	NS
Hammerschlag et al. (90)	2/6 (33%)	1/6 (16%)
Frommell et al. (92)	7/18 (39%)	2/18 (11%)
Heggie et al. (94)	20/95 (21%)	3/95 (3%)
Hammerschlag (297)	12/36 (33%)	3/36 (8%)
Mardh et al. (287)	5/23 (23%)	NS
Grossman et al. (97)	16/89 (18%)	16/89 (18%)
Schachter et al. (282)	23/131 (18%)	21/131 (16%)
Ismail et al. (284)	11/36 (31%)	5/36 (14%)
Schaefer et al. (294)	13/61 (21%)	14/61 (23%)

TABLE 5.10. *CHLAMYDIA TRACHOMATIS* INFECTION AMONG INFANTS BORN TO CHLAMYDIAL-INFECTED MOTHERS

Conjunctivitis

Acute conjunctivitis of the newborn (inclusion conjunctivitis of the newborn or inclusion blennorrhea) was first described in 1910. It was recognized that the agent causing inclusion conjunctivitis of the newborn also was present in the genital tract of the mother. Intracytoplasmic inclusions similar to those produced by trachoma were seen in scrapings of the conjunctiva of infants with conjunctivitis and in those from the cervix of their mothers. This mucopurulent conjunctivitis generally develops 5 to 14 days after birth. Usually the organism is not identified in the conjunctiva during the first 24 hours of life. It now is recognized as the most common conjunctivitis in the first month of life (295). Approximately one third of infants exposed to *C. trachomatis* during vaginal delivery develop chlamydial conjunctivitis (90,92,94,97,98,282,287).

The organism replicates extensively in superficial epithelial cells of the conjunctiva and causes considerable cell damage. There is an exuberant inflammatory reaction, and pseudomembranes may form (which may result in scar formations). Follicles such as those seen in adults or older children with chlamydial infection of the conjunctiva usually are not observed unless the disease has been active for 1 to 2 months. The majority of untreated infants will resolve spontaneously during the first few months of life. Occasionally, some infants maintain persistent conjunctivitis; pannus formation and scarring typical of trachoma have been reported. Visual loss is rare. Micropannus and some scarring most likely will occur in infants if they are not treated within the first 2 weeks of the disease. No sequelae will develop if the infants are treated early.

The disease often starts with a watery eye discharge that rapidly and progressively becomes very purulent. The eyelids usually are markedly swollen. The conjunctivae become very reddened and somewhat thickened throughout. The follicular nature of the infection that is so characteristic of trachoma is missing, because the conjunctivae of the neonate lacks lymphoid tissue.

In severe cases, diagnosis is readily made by demonstrating the typical inclusion bodies by Giemsa stain of conjunctival scrapings. The chlamydial organisms also are readily cultured from the eye. Currently, the antigen detection tests (e.g., direct fluorescent monoclonal antibody [DFA], enzyme immunoassay [EIA], and DNA probe) are the most widely used diagnostic tests for *C. trachomatis* (296). However, nucleic acid amplification testing (PCR, LCR, TMA) is increasingly replacing these tests. Serologic diagnosis is not helpful because of the presence of maternally transmitted antichlamydial IgG antibody and the uncertain appearance of IgM in this disease. Because chlamydial infections appear to be unaffected by silver nitrate prophylaxis, it is recommended that a prophylactic regimen active against both chlamydia and gonococci be used in neonates. Erythromycin and tetracycline ointment has been shown to prevent development of inclusion conjunctivitis of the newborn (297,298); however, the regimen does not affect chlamydial infection in

extraocular sites in infants (299,300). The preferred method for prevention of neonatal chlamydial conjunctivitis is prevention of vertical transmission from infected mothers during the birth process. This involves routine screening pregnant women for *C. trachomatis* and treating those infected with chlamydia prior to delivery. Such an approach currently is recommended by the CDC (54).

Pneumonia

Until 1975, it was assumed that chlamydial infection in the infant was restricted to the conjunctiva. During a prospective study on the development of inclusion conjunctivitis of the newborn, an infant who had been treated successfully for conjunctivitis developed pneumonia and yielded chlamydia from the respiratory tract (295). In 1977, Beem and Saxon (301) reported a series of retrospective and prospective cases of chlamydial pneumonia in young infants. This report was followed by reported studies from other centers (91,302), and the clinical entity of chlamydial pneumonia became well defined. During the ensuing years, it has become clear that this disease is very common, probably one of the three most common pneumonias seen in infancy. The many reported series have helped to delineate the clinical features of this infection (301,302 and 303).

Of the vast majority of chlamydial pneumonia cases present between weeks 4 and 11 of life, virtually all will be symptomatic before week 8. Initially, these infants present with upper respiratory symptoms. The infants usually are afebrile or have only a minimal amount of fever. The upper respiratory tract symptoms are those of congestion and obstruction of the nasal passages without significant discharge. The finding of abnormal bulging eardrums is common, occurring in more than half of the cases described. A history of conjunctivitis can be elucidated in half the cases. Thus, it is important to recognize that antecedent chlamydial conjunctivitis is not required for chlamydial pneumonia to develop. Lower respiratory tract symptoms consist of tachypnea and a very prominent staccato-type cough. Some infants have apneic periods. Crepitant inspiratory rales are commonly heard; on the other hand, expiratory wheezes are uncommon. The radiographic findings are those of hyperexpansion of the lungs, with bilateral symmetrical interstitial infiltrates.

Laboratory findings include a normal white blood count and an increased number of eosinophils. Blood gas analysis usually shows that many of the infants have a mild or moderate degree of hypoxia. Serum immunoglobulins, both IgG and IgM, generally are elevated.

Initially, it was speculated that chlamydia pneumonia of infants resulted from *C. trachomatis* draining into the respiratory tract from involved conjunctivae and that the eye was the portal of entry. Prospective studies have shown that conjunctivitis is not a prerequisite, and prevention of conjunctivitis by appropriate ocular prophylaxis does not prevent respiratory tract infection and pneumonia (297,298,299 and 300). Although it seems likely that some respiratory tract infections may result from conjunctivae seeding at birth, it is apparent that the respiratory tract can be directly infected during the birth process. Hammerschlag et al. (297) showed that neonatal prophylaxis with erythromycin ointment could prevent the development of inclusion conjunctivitis of newborn (ICN) but had no apparent effect on nasopharyngeal infection or pneumonia.

The long incubation period for chlamydial pneumonia in infants seen in most cases is

perplexing. There have been some suggestions in the literature that the pneumonia in infants likely reflects a hypersensitivity response to the organism in the lung. Although it is clear that the host inflammatory reaction is a major contributing factor in any disease process, there is scant evidence to support chlamydia pneumonia of infants as a hypersensitivity reaction. The speculation is based in large part on the relative eosinophilia seen in some cases and the difficulties in obtaining appropriate lung specimens for isolation attempts or sequential pathologic analysis of the development of the disease. Arth and colleagues (304) recovered *C. trachomatis* from three of the four lung specimens tested from infants with chlamydial pneumonia. These data support the assertion that *C. trachomatis* is a causative agent for pneumonia in human infants. Isolation of chlamydia from a defined clinical syndrome, such as described by Beem and Saxon (301), and the findings of high antibody levels in the sera of patients with this syndrome suggest that *C. trachomatis* is one of the major causes of infant pneumonia.

Diagnosis of chlamydial pneumonia in the young infant is based on the typical clinical presentation, chest radiograph with bilateral presentation, and significant increase in, or high levels of, IgM antibody to *C. trachomatis* (296). Although an acute IgM antibody titer ³1:32 is strongly suggestive of chlamydial pneumonia, a definitive diagnosis is made by culturing *C. trachomatis* from the respiratory tract (nasopharynx) or lung (296). Nonculture tests for chlamydial infection have lower sensitivity and specificity for specimens from the upper respiratory tract than for ocular or genital tract specimens (54). Cross-reaction with *C. pneumoniae* leads to false-positive nonculture testing in respiratory tract specimens.

Erythromycin 50 mg/kg/day orally divided into four doses for 10 to 14 days is the recommended treatment for chlamydial pneumonia in infants (54). The CDC reports that this regimen is approximately 80% effective and that a second course of therapy may be required (54).

Other Clinical Manifestations In The Neonate

Serologic evidence of infection with chlamydia is present in 60% to 70% of infants passing through an infected cervix (90,91,92 and 93). Although conjunctivitis and pneumonia are the only two firmly established and clearly delineated clinical entities, there is evidence suggesting that chlamydia plays a role in otitis media, obstruction of nasal passages, and lower airway disease (bronchiolitis) in young infants. In addition, colonization of the gastrointestinal tract occurs (91). It is clear that many infants, as well as older children, acquire antibodies to *C. trachomatis* without having experienced a discrete and recognized infection, suggesting that there may be other, not yet described, clinical entities caused by this organism.

Infections In Pregnant Women

Postpartum Endometritis

An association between *C. trachomatis* and postpartum infection initially was described in the ophthalmology literature in 1936, when Thygeson and Mengert (150) reported that the mothers of newborns with inclusion conjunctivitis were at increased risk for postpartum PID. Similarly, Mordhorst and Dawson (151) noted an association between neonatal inclusion conjunctivitis and development of postpartum

infections in the mothers of infected newborns. In a subsequent prospective investigation, Wager and coworkers (306) from Seattle, Washington, suggested that pregnant women in whom *C. trachomatis* was recovered at their initial prenatal visit were at significant increased risk to develop late-onset endometritis following a vaginal delivery. Late endometritis developed in 7 (22%) of 32 women with *C. trachomatis* isolated during prenatal care, compared with 18 (5%) of 359 chlamydia-negative women. However, attempts to recover chlamydia from the patients during their acute infection were not performed. Cytryn et al. (307) reported the occurrence of severe pelvic infection from *C. trachomatis* after cesarean section. Ismail et al. (284) and Hoyme et al. (308) confirmed the finding of Wager et al. that there was an increased risk for postvaginal delivery endometritis in chlamydial-infected women. Plummer et al. (309) demonstrated that *C. trachomatis* is a significant risk factor for development of postpartum genital tract infection. In particular, these authors noted that postpartum salpingitis was significantly associated with the presence of maternal chlamydial infection (OR, 3.6; $p < 0.01$) (309). However, a number of studies did not confirm any association between *C. trachomatis* and the development of postpartum endometritis (94,288,289 and 290,310,311 and 312). Gencay et al. (313) performed a serologic assessment in mothers whose children were admitted to the neonatal intensive care unit of Children's Hospital in Helsinki. The frequency of maternal infection (fever and vaginal discharge) was significantly higher (7% vs. 3%) in the IgM-seropositive group compared to the IgM-seronegative group. However, this study provides only indirect evidence that *C. trachomatis* is a putative agent in postpartum endometritis. Elucidation of the role this organism plays as a causative agent in postpartum endometritis awaits further prospective studies using chlamydia detection techniques during the acute infection.

Postabortion Endometritis

Several studies demonstrated that patients with chlamydial cervicitis who undergo pregnancy termination are at high risk for postabortion endometritis (314,315,316,317 and 318). Approximately 10% to 35% of women with cervical *C. trachomatis* at the time of elective abortion develop postabortal pelvic infection compared to 2% to 10% of chlamydia-negative women. Moller et al. (314) demonstrated that treatment of chlamydial infection before the procedure prevented postabortion endometritis. For this reason, either screening and treatment for chlamydia before the procedure or prophylaxis with doxycycline or azithromycin at the time of termination should be done in patients at high risk for *C. trachomatis*.

Spontaneous Abortion And Fetal Death

Martin and colleagues (95) in Seattle, Washington, reported a significant increase in the occurrence of spontaneous abortions and fetal deaths among women who had *C. trachomatis* recovered from the cervix at their initial prenatal visit. Proof of causation for these events is not available and requires additional large-scale prospective investigations. In our prospective studies in San Francisco of vertical transmission from mothers to neonates of *C. trachomatis*, we were unable to corroborate these findings (*unpublished data*). Similarly, Harrison et al. (289) noted no increased risk for spontaneous abortion or fetal deaths among women with chlamydial infections. However, Witkin and Ledger (262) reported that high-titer IgG antibody to *C. trachomatis* was significantly associated with recurrent spontaneous abortion (31.8% in women with three or more spontaneous abortions vs. 7.5% in

seronegative women). Subsequently, Rae et al. (319) in Edinburgh and Paukku et al. (320) in Finland failed to demonstrate an association between serum antibodies to *C. trachomatis* and recurrent pregnancy loss.

Prematurity, Low Birthweight, and Premature Rupture of the Membranes

A great deal of interest and controversy have revolved around what role, if any, *C. trachomatis* infection of the cervix plays in the etiology of preterm labor and delivery, low birthweight, and PROM. Once again, conflicting studies exist (Table 5.11) (321). Martin and coworkers (95) in Seattle, Washington, noted a significant increase in the occurrence of preterm delivery among chlamydia-positive women. They also reported an increased incidence of low birthweight babies and of perinatal mortality in the chlamydia-positive group; the major cause of mortality was intrauterine death. In this study, only women seen before 18 weeks' gestation were included. Of the 18 women with chlamydia isolated, stillbirth occurred in three and preterm delivery and perinatal death in another three; thus, there was a 33% incidence of perinatal mortality in the Seattle study. This is in significant contrast with results from the 238 uninfected mothers, of whom only eight (3%) had similar complications. In the chlamydia-infected group, the incidence of preterm delivery at less than 37 weeks was 28% versus 6% in uninfected women and at less than 30 weeks was 28% versus 3%. Birthweight less than 2,500 g was present in 28% of infected women versus 8% of uninfected women. Subsequent studies performed at many sites from a wide geographic distribution failed to confirm these findings. Harrison et al. (289), Thompson et al. (288), Hardy et al. (293), Heggie et al. (94), Berman et al. (311), Ismail et al. (284), and McGregor et al. (312) reported no association between *C. trachomatis* cervical infection and prematurity, low birthweight, stillbirths, or PROM.

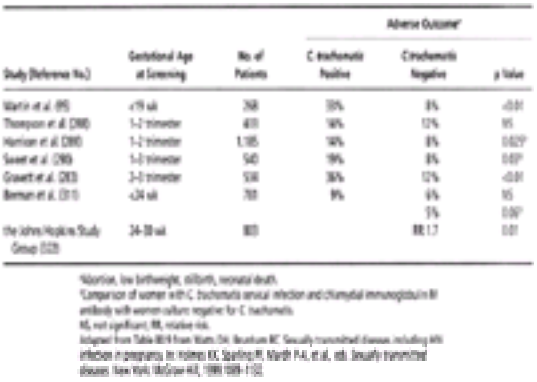


TABLE 5.11. COHORT STUDIES OF THE EFFECTS OF *CHLAMYDIA TRACHOMATIS* ON PREGNANCY OUTCOME

Of considerable interest was the finding by Harrison and colleagues (289) that there was a subset of chlamydia-positive mothers who showed evidence of active invasive infection manifested by the presence of significant titers of IgM antibody against *C. trachomatis.* In this subgroup, there was significantly increased incidence of low birthweight, shorter gestational length, and more PROM. Sweet et al. (290) confirmed that the subset of women with cervical chlamydial infection and IgM

seropositivity against *C. trachomatis* were at significant increased risk for preterm delivery and PROM. In the chlamydia-infected women who were IgM-positive, preterm delivery occurred in 13 (19%) of 67 IgM-positive women versus eight (8%) of 99 IgM-negative women ($p = 0.03$). Similarly, Berman et al. (311) confirmed the association of premature birth with IgM seropositivity among *C. trachomatis* culture-positive pregnant women. In a multivariate analysis of their cohort study, Gravett et al. (283) reported that cervical infection with *C. trachomatis* was independently associated with preterm PROM, preterm labor, and low birthweight. Similarly, Martius et al. (323), in a case-control study, found an increased association between chlamydia and preterm birth (OR, 5.4; 95% CI, 1.3–23.4) that was independent of bacterial vaginosis, lactobacillus, or PROM. Alger and colleagues (324) reported that preterm PROM occurred in 23 (44%) of 52 chlamydia-positive women versus 13 (15.5%) of 84 controls. Using a 90% confidence interval as significant, the Johns Hopkins Study Group (322) demonstrated that *C. trachomatis* was significantly associated with preterm birth (OR, 1.6; 90% CI, 1.01–2.5) and intrauterine growth retardation (OR, 2.4; 90% CI, 1.32–4.18).

Two treatment trials of chlamydial infection in pregnancy provided additional support for the role of *C. trachomatis* infection in the etiology of PROM, preterm labor, and preterm delivery. Ryan et al. (291) reported that, in a high-risk population with a chlamydia prevalence rate of 21%, pregnant women infected with *C. trachomatis* and treated with erythromycin had significantly lower incidences of PROM, low birthweight, and perinatal death compared to untreated infected women or uninfected female controls. Using untreated historical controls from the first 16 months of the study when cervical cultures were performed on all new obstetric patients to determine the prevalence of *C. trachomatis* infection, these authors reported that PROM occurred in 58 (5.2%) of 1,052 untreated chlamydia-positive women, 39 (2.9%) of treated chlamydia-positive women, and 243 (2.7%) of 8,868 chlamydia-negative pregnant women (untreated positive vs. negative, $p < 0.001$; untreated positive vs. treated positive, $p < 0.0001$). Similarly, birthweight less than 2,500 g occurred in 218 (19.6%) of 892 untreated chlamydia-positive women, 145 (11.0%) of 1,178 treated chlamydia-positive women, and 1,068 (11.7%) of 8,043 chlamydia-negative women (untreated positive vs. negative, $p < 0.001$; untreated positive vs. treated, $p < 0.001$). Cohen et al. (292) compared pregnancy outcomes of women treated successfully with erythromycin, chlamydia-infected women who did not comply with or respond to treatment, and uninfected women. For the successful group versus the treatment failure group, they reported that the rate of preterm delivery was 3% versus 14%, ROM 7% versus 20%, preterm labor 4% versus 24%, and intrauterine growth retardation 13% versus 25%. Concern with this study revolves around the issue of compliance, and that compliant patients most likely are different from noncompliant individuals. Unfortunately, no well-designed, prospective, double-blinded, placebo-controlled treatment trials of chlamydial infection in pregnancy have been reported. It is unlikely that such a study will ever be undertaken due to ethical considerations revolving around the issue of not treating documented cervical chlamydial infection.

Only large-scale prospective investigations will determine the role of *C. trachomatis* as a cause of preterm labor and delivery, low birthweight, and/or perinatal loss. A large prospective study, The Vaginal Infections and Prematurity Study, has been undertaken by the National Institutes of Health (325). Nugent et al. (326) reported preliminary results on the association between chlamydial infection and adverse pregnancy outcome. Univariate analysis indicated that low birthweight (OR, 1.6; 95% CI, 1.3–2.1) and preterm delivery (OR, 1.6; 95% CI, 1.3–2.0) were more likely to

occur in chlamydial-infected women. In the multivariate analysis, which controlled for age, marital status, ethnicity, and presence of other organisms, the adjusted odds ratio for preterm delivery was 1.53 (95% CI, 1.21–1.93). No serologic data from this large database have yet been reported. When final analysis is complete, the large multicenter study sponsored by the National Institute of Child Health and Human Development should provide a more definitive determination of the role *C. trachomatis* plays in causing adverse outcomes of pregnancy (321).

DIAGNOSIS OF CHLAMYDIAL INFECTIONS

The principles for diagnosing chlamydial infections are essentially the same as those for diagnosing any other microbial infection (84). The agent can be demonstrated by cytology on clinical specimens, and serologic assays can be used to demonstrate increasing antibody titers to chlamydial antigens. Until recently, the “gold standard” approach to laboratory diagnosis of *C. trachomatis* relied on cell culture. During the 1980s, antigen and nucleic acid detection methods were introduced into clinical practice for diagnosing genital chlamydial infection (327,328,329 and 330). They rapidly became the most widely available diagnostic tests for detection of *C. trachomatis* because of their lower costs, less need for expertise, preservation of infectivity during transport, and shorter time required for results (84). Nucleic acid amplification technology now is available for detection of *C. trachomatis* (331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350 and 351).

Specimens must be appropriately collected and transported to optimize detection of *C. trachomatis* by culture, antigen detection, DNA probe, or nucleic acid amplification. *Chlamydia trachomatis* is an obligate intracellular pathogen and thus is best isolated from cell scrapings from the endocervix or urethra rather than from purulent discharge, secretions, or urine. Swabs have traditionally been used to obtain specimens, but a cytologic brush is preferred for endocervical specimens. Before obtaining endocervical specimens, mucus and debris should be removed from the external cervical using a swab. Wooden-shafted swabs reduce the number of chlamydia inclusion-forming units and should not be used. Rayon-, cotton-, or calcium alginate-tipped swabs can be used. Some lots of calcium alginate swabs have depressed recovery of *C. trachomatis* and thus should be used only in settings where quality control mechanisms are in place to prevent such an occurrence.

Specimens for culture are placed immediately into a transport medium (sucrose phosphate) containing antimicrobial agents (usually gentamicin, vancomycin, and nystatin). The specimen should be refrigerated, transported on ice, and inoculated as soon as possible, preferably within 24 hours. If these requirements cannot be met, the specimen should be frozen at –70°C until it can be inoculated. With antigen detection methods, DNA probes, and nucleic acid amplification, test swabs should be placed in the manufacturer's transport medium and processed as directed.

Cytology

Both the intracellular nature of chlamydiae and their unique growth cycle provide specific markers for cytologic diagnosis. Before the availability of cultures, demonstration of inclusions in scrapings from genital tract specimens was the method used to elucidate the epidemiology and clinical spectrum of chlamydial

infections. These procedures cannot be recommended because of their poor sensitivity and specificity compared to culture, antigen detection methods, DNA probe, and nucleic acid amplification for detection of genital tract chlamydia. Schachter and Dawson (352) reported that cervical infection with chlamydia can be recognized only by cytologic means in approximately 20% of cases. In a correlative study of Pap smear, fluorescent antibody, and culture for the diagnosis of *C. trachomatis*, Spence and coworkers (353) reconfirmed the poor sensitivity and specificity of cytology. However, it is a useful and sensitive means for diagnosing inclusion conjunctivitis of the newborn.

Serology

Despite an abundant immune response to chlamydial infections (6), serology is not particularly useful for diagnosing non-LGV strains of *C. trachomatis* infections of the genital tract (354). Virtually all individuals who are not treated very early in the course of their infection will develop a measurable antibody response. A cell-mediated immune response also is stimulated (355). The high background rates of antichlamydial antibodies in sexually active populations render serodiagnosis inconclusive. Because many chlamydial infections are chronic, the patients may not be seen at an appropriate time for collection of acute and convalescent sera to document increasing titers. It is important to recognize that a single antibody titer as a screening procedure will suggest previous chlamydial infection but not active infection. The exception would be extremely high IgG or IgM levels. Immunoglobulin M antibodies or fourfold rises in IgG titer usually are considered diagnostic of recent *C. trachomatis* infection. Unfortunately, they are detected infrequently in patients with uncomplicated genital infections (356).

The two serologic tests that have been used for chlamydial infections are the complement fixation (CF) test and the microimmunofluorescent (Micro-IF) test. The CF test is most useful for diagnosing LGV. The Micro-IF test is a much more sensitive test for diagnosing *C. trachomatis* and allows determination of the immunoglobulin class of antibody. It is possible that, in some specific clinical instances, serologic tests may be helpful to the clinician in diagnosing chlamydial infection. For example, in an adult's first acquisition of chlamydia, paired sera will show increasing titers. In some diseases involving systemic complications of superficial chlamydial infections, an exceptionally high titer may provide some corroboration for clinical diagnosis (91,157,301). For example, women who develop acute salpingitis from a chlamydial infection will have much higher antibody levels than women with uncomplicated cervicitis. Men with chlamydial epididymitis will have much higher antibody titers than men with chlamydial urethritis. A similar pattern is seen in infants with perinatally acquired infection. An infant with pneumonia will have much higher antibody titers than a child with uncomplicated conjunctivitis (91,301). The serologic test of choice is the Micro-IF test of Wang and Grayston (354).

The recently described *C. pneumoniae* (TWAR) strain of chlamydia is diagnosed serologically. Care must be taken to exclude *C. pneumoniae* (TWAR) from *C. trachomatis*. This is crucial, because *C. pneumoniae* infections are very common.

Culture Methods

Until recently, the optimum laboratory test on a routine basis for the diagnosis of chlamydial infections of the female genital tract was isolation of the organism from

the involved site. Culture was viewed as the “gold” standard against which all other diagnostic methods were compared. Because chlamydiae are obligatory intracellular parasites, isolation attempts cannot be performed on artificial media; they require a susceptible tissue culture cell line. The methods of choice involve treating a susceptible cell monolayer with an antimetabolite that interferes with the replication or metabolism of the host cell, while allowing chlamydial functions. Two of the most commonly used methods are treatment of McCoy cells with 5-iodo-2-deoxyuridine and treatment with cycloheximide (84,357,358). The most important step in the isolation procedure involves centrifuging the organisms onto the cell monolayers; this method has increased the sensitivity of the cell culture method 100-fold. Cycloheximide treatment appears to be simple, inexpensive, and, above all, the most sensitive. After an appropriate incubation period that varies from 24 to 72 hours, depending on the staining procedures used, the monolayers are stained and examined microscopically for the presence of inclusions. This can be done with iodine, Giemsa stain, or fluorescent-labeled monoclonal antibody (Fig. 5.6). This last method is the preferred approach in most laboratories. Although isolation procedures for *C. trachomatis* are useful for diagnosis on a routine basis, the isolation procedures are not without drawbacks. The involved anatomic site must be appropriately sampled. Culture of discharges is inadequate, and an adequate sample of involved epithelial cells must be obtained. The specificity of culture approaches 100%, but the sensitivity of chlamydial culture techniques is less well delineated. Before the introduction of nucleic acid amplification technology, Schachter and Grossman (18) estimated that the sensitivity of culture techniques for NGU or cervicitis was 70% to 80%. In laboratories that use a blind second passage for negative specimens, another 10% to 20% positive cultures will be identified on the second passage. Moncada et al. (359) reported that use of a cytobrush to obtain an endocervical specimen significantly improved the sensitivity of culture.

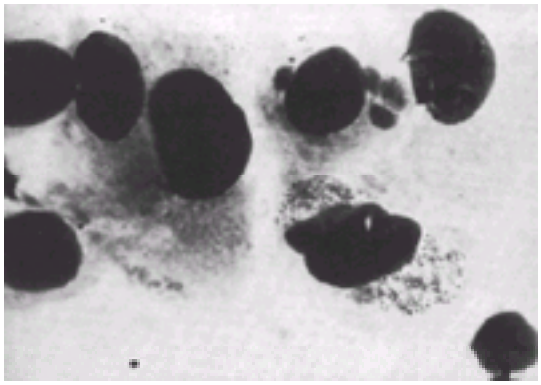


FIGURE 5.6. Giemsa stain demonstrating *Chlamydia trachomatis* inclusions.

Culture has the advantage that it preserves organisms for further studies, including antimicrobial susceptibility testing and genotyping (84). Because it detects only viable chlamydial elementary bodies and is unlikely to be contaminated, culture remains the standard for medicolegal matters, such as sexual abuse in adults or children (84). However, there are multiple disadvantages that limit the use of culture, including (i) its relative insensitivity (65% to 85%) compared to nucleic acid

amplification techniques, even in the hands of very experienced laboratories (337,341,342); (ii) cold chain transport of specimens; (iii) expense; (iv) delay in obtaining results (3 to 7 days); and (v) need for substantial technical expertise (84). Because of these limitations and with the advent of nucleic acid amplification techniques, culture now is used infrequently and usually is performed only in reference laboratories (84).

Nonculture Methods

Nonculture, non-nucleic acid amplification testing is based on direct visualization of chlamydia by staining with fluorescein-labeled specific antibodies (DFA), immunohistochemical detection of antigen (EIA and rapid tests), and detection of hybridization to a DNA probe (84). The advantages of these nonculture, non-nucleic acid amplification techniques include (i) ability to use laboratories that lack the expertise or facilities to perform culture; (ii) specimen transport is less rigorous; and (iii) the technology is standardized (84). Multiple investigations have compared these tests favorably to culture (84). As a result, most laboratories in North America and western Europe use antigen detection tests (DFA and EIA) or nucleic acid hybridization tests (DNA probe) (351). Chernesky et al. (351) estimated that approximately 70% of patients are tested for *C. trachomatis* by antigen detection or nucleic acid hybridization and less than 2% are cultured.

However, as pointed out by Black, additional consideration must be given to interpreting the results of these tests due to their reduced sensitivity and specificity compared to culture and even more so when compared to nucleic acid amplification techniques (84). In particular, the sensitivities of nonculture, non-nucleic acid amplification tests may be overestimated when both the culture and the nonculture test miss a true infection (84). In addition, use of nonculture, non-nucleic acid amplification techniques in populations with a low prevalence of infection (less than 8%) is problematic, as the proportion of false-positive results increases as the prevalence of infection decreases.

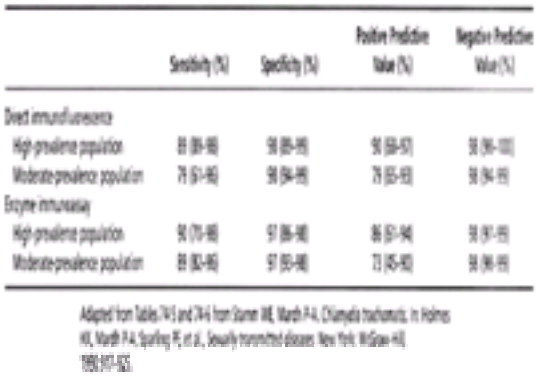
Antigen Detection

The need for a more readily available, less expensive, and rapid diagnostic test for chlamydia led to the development of antigen detection methods for *C. trachomatis* that were introduced into clinical practice in the 1980s. The most widely used antigen detection tests for *C. trachomatis* are DFA staining of chlamydial elementary bodies in smears obtained from clinical specimens and EIA.

In general, DFA staining in the hands of an experienced technician has sensitivity of 80% to 85% and specificity greater than 99% compared with cell culture (6,84,360,361,362,363 and 364). Great skill and experience are required to obtain specimens and evaluate the slides. The generally accepted criterion for a positive DFA test is the presence of ten or more elementary bodies (84). Despite its high specificity and ability to verify the adequacy of the specimen, the labor and skill required to perform the DFA test preclude its use with large volumes of specimens (84). However, the DFA test has found a niche as a confirmatory test for positive results of other nonculture chlamydia tests and in discrepancy analysis for nucleic acid amplification tests (84).

The EIA method has a sensitivity in the range from 60% to 80% compared to culture (84,364,365 and 366). However, with the EIA test, antibodies to chlamydial LPS may cross-react with LPS of other Gram-negative bacteria from the vagina and produce false-positive results. This decreases the specificity of the test (6,84). These false-positive results can be eliminated by using either a confirmatory assay with a blocking antibody or with DFA (6,84,367). Without the use of an antibody-blocking reagent, the specificity of EIA is about 97%. Confirmation with an antibody-blocking reagent improves the specificity to greater than 99% (84). Similar results are obtained using a DFA test for confirmation (84,368,369).

Both antigen detection methods have several advantages over culture. They are less expensive, do not require maintenance of cold chain to store specimens en route to the laboratory, can be performed more rapidly, and, for DFA testing, have a built-in quality control (e.g., presence of epithelial cells on the smear). However, both methods have a false-positive rate of 2% to 3%. As a result, despite excellent sensitivity and specificity, the positive predictive value of antigen detection methods decreases in low-prevalence populations. In a population with a prevalence of 2% to 3%, a positive result by antigen detection will be correct in only about one half of instances. As shown in Table 5.12, even in a moderate-prevalence population, both direct immunofluorescence and EIA tests have a lower and wide range of positive predictive values.



	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Direct immunofluorescence				
High-prevalence population	[illegible]	[illegible]	[illegible]	[illegible]
Moderate-prevalence population	[illegible]	[illegible]	[illegible]	[illegible]
Enzyme immunoassay				
High-prevalence population	[illegible]	[illegible]	[illegible]	[illegible]
Moderate-prevalence population	[illegible]	[illegible]	[illegible]	[illegible]

Adapted from Tables 74-1 and 74-4 from Stamm WE, Wardh P-A, Chlamydia trachomatis. In Holmes KK, Wardh P-A, Spaulding PF, et al., Sexually transmitted diseases. New York: McGraw-Hill, [illegible].

TABLE 5.12. REPORTED EXPERIENCE WITH ANTIGEN DETECTION METHODS FOR *CHLAMYDIA TRACHOMATIS* FROM THE ENDOCERVIX IN WOMEN

Similar to the situation with tissue culture, using a cytobrush to collect cervical specimens for detection of *C. trachomatis* significantly improved the sensitivity of antigen detection tests (359). Although initially used only in nonpregnant women to obtain cervical specimens for this purpose, the cytobrush has been shown to be safe for use in pregnant women. Chlamydiazyme (Abbott Diagnostics, North Chicago, IL) was the first available and most widely used and studied EIA. Based on numerous studies comparing Chlamydiazyme to culture and expanded standards, the sensitivity and specificity of Chlamydiazyme are 73% and 98%, respectively (84). A more recently introduced EIA for *C. trachomatis* is the MicroTrak EIA (Behring). The reported overall sensitivity and specificity of MicroTrak EIA compared to culture or an

expanded culture standard for endocervical specimens are 83% and 98% to 99%, respectively. The specificity of this test can be improved by confirmation using the MicroTrak DFA test (368). Several studies demonstrated that the performance of the MicroTrak EIA is superior to Chlamydiazyme (369,370 and 371).

Rapid office-based direct EIA kits have been developed for detection of *C. trachomatis.* The results are read visually, usually in about 30 minutes. Like laboratory EIAs, the rapid tests use antibodies against LPS and thus may cross-react with LPS of other microorganisms (84). Examples of commercially available rapid tests for chlamydia include Testpack (Abbott Diagnostics) (372,373). Clearview (Unipath Ltd., Bedford, United Kingdom) (374,375), and Surecell (Johnson & Johnson, Rochester, NY) (376). In general, the rapid tests have proven to be less sensitive and specific than laboratory-performed EIAs or the PACE 2 DNA probe (84). The reported sensitivity of rapid tests relative to culture ranges from 52% to 85% for endocervical swabs. Reported specificity is greater than 95% (372,374,375 and 376). These values reflect optimal results because the tests were performed by experienced personnel (84).

DNA Probe Assays

The PACE 2 test (Gen-Probe, San Diego, CA) is the only commercially available DNA probe for detection of *C. trachomatis.* This DNA probe uses nucleic acid hybridization to identify *C. trachomatis* DNA directly from urogenital swab specimens. The DNA probe is approximately 1 log unit more sensitive than EIA technology and detects approximately 10^3 chlamydial elementary bodies (Fig. 5.7) (84). The clinical sensitivity of PACE 2 is similar to that of the better EIAs (84), with an overall sensitivity and specificity of 85% and 98% to 99%, respectively (329,330,374,377,378). A limited number of studies have assessed the sensitivity of PACE 2 compared to nucleic acid amplification technology; in these studies, the sensitivity of PACE 2 ranged from 77% to 93% (377,379).

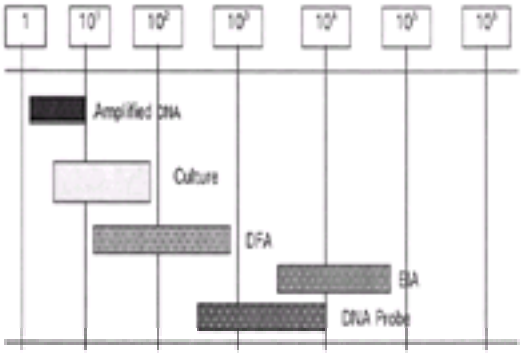


FIGURE 5.7. Relative limits of detection for different technologies used to diagnose *Chlamydia trachomatis* (log number chlamydial elementary bodies).

An important advantage of the PACE 2 test is that it can be used in conjunction with

a probe for detection of *N. gonorrhoeae* as a single-swab specimen (84). In addition, PACE 2 does not require cold chain transportation, specimens remain stable in storage, minimal technical expertise is required, and testing procedures can be automated, which leads to decreased costs. Black (84) noted that the PACE 2 test is probably the most commonly used test for detecting *C. trachomatis* in public health laboratories in the United States. However, PACE 2 is less sensitive than nucleic acid amplification technologies, and the CDC recommends that positive results in a low-prevalence population be confirmed (2).

Nucleic Acid Amplification Tests

The most important recent advance in the diagnosis of chlamydial infections of the genital tract has been development of tests using nucleic acid amplification technology (6,8,84). Nucleic acid amplification testing is extremely sensitive (detects as little as a single gene copy) and highly specific (Fig. 5.7) (84). These characteristics provide the opportunity to use these tests for noninvasive (urine or vaginal swab) specimen procurement to screen asymptomatic men and women for chlamydial infection (6,8,84). Moreover, nucleic acid amplification tests using noninvasive sampling have been shown to provide improved results over invasive sampling with culture, antigen detection, or DNA probe (84,336,342). The two most widely used nucleic acid amplification tests are PCR and LCR, which target nucleotide sequences on the plasmid of *C. trachomatis* present in multiple copies within each elementary body. The third methodology now available is the TMA test, which amplifies chlamydial ribosomal RNA. The lower limit of detection for these tests is in the range from 1 to 10 elementary bodies (Fig. 5.7). In comparison, EIA requires 10,000 elementary bodies, DNA probe requires 1,000, and culture requires 10 to 100.

Because the nucleic acid amplification tests are so sensitive, a new gold standard other than cell culture is necessary (6,342). Consequently, specimens that are negative on culture but positive on nucleic acid amplification test require additional evaluation (84). Confirmation is first attempted using DFA. If this result also is negative, the nucleic acid amplification test is repeated with a probe directed against a different nucleotide target sequence, the chromosomal MOMP gene sequence (84).

Nucleic acid amplification technologies detect DNA or RNA targets and do not require the presence of viable or intact organisms for a positive test (84). This has major implications when considering “test of cure.” It has been suggested that a culture-negative, nucleic acid-positive state following appropriate treatment lasts up to 3 weeks, after which both culture and the nucleic acid amplification test will be negative.

Polymerase Chain Reaction

Polymerase chain reaction is able to multiply a specific sequence of DNA to 10^5-fold or greater (331). It has become a very powerful tool for identifying infecting agents. Since approval by the U.S. Food and Drug Administration (FDA) in 1993, the Amplicor PCR test (Roche Diagnostics) has been widely used in the United States (6,331,332,333,334,335 and 336,339,377,380,381,382,383 and 384). Reported studies demonstrated that Amplicor PCR has an overall sensitivity of 90% and specificity of 99% to 100% (334,335,339,377,380,381 and 382). The Amplicor PCR is

approved for cervical, male urethral, and male urine specimens (6). As discussed earlier, the exquisite sensitivity of nucleic acid amplification tests has allowed use of first-void urine in men and women as a noninvasive specimen for detection of *C. trachomatis* in screening programs (6,8,84). Studies evaluating PCR detection of *C. trachomatis* in urine versus urethral or endocervical specimens demonstrated sensitivity of 92% to 96% and specificity of 98% to 99% (335,339,381,382). Most exciting has been the novel approach in which vaginal swabs, particularly self-obtained swabs, have been used with PCR testing in screening programs (337,338). In the study by Wiesenfeld et al. (337), the sensitivity of vaginal swabs obtained by health care workers was 92%, which was greater than that seen with PCR, culture, or EIA of the cervix or urethra. In patients, self-collected vaginal swabs demonstrated a sensitivity of 81% with PCR (337). The PCR appears to be a simple, accurate, and reliable test for detection of *C. trachomatis,* even in low-prevalence, asymptomatic populations.

Ligase Chain Reaction

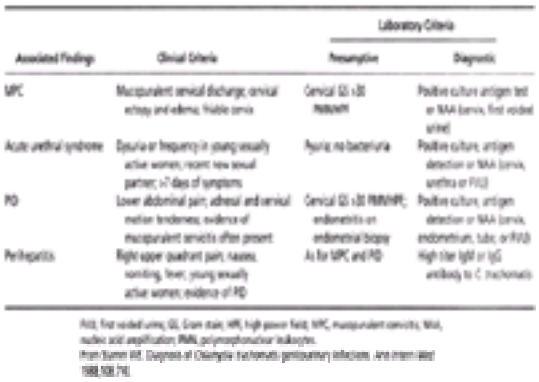
The second nucleic acid amplification technique to become available for the diagnosis of *C. trachomatis* is LCR (Abbott Diagnostics) (385). LCR was approved by the FDA in 1995 as a diagnostic test for chlamydia. Initial studies assessing LCR demonstrated an overall sensitivity of 94% and specificity of 99% to 100% (84,341,342,386,387 and 388). In studies using endocervical specimens, Schachter et al. (341) and Bassiri et al. (388) reported sensitivity of 94% and 87%, respectively, and specificity of 100%. Studies using first-void urine demonstrated sensitivity of 93% to 98% and specificity from 99% to 100% (342,386,387). Compared with cell culture, LCR generally detects 15% to 40% more infected persons, resulting in an increased prevalence of 4% to 5% (8,342).

Transcription-mediated amplification (AMPT CT; Gen-Probe) was the third nucleic acid amplification test approved by the FDA for detection of *C. trachomatis* (84,389). The TMA test targets 16s rRNA. Experience with this test is limited to date. Several other nucleic acid amplification tests are at various stages of development. These include (i) strand displacement amplification (SDA; Becton-Dickinson), which targets DNA; (ii) nucleic acid sequence-based amplification (NASBA; Organon-Teknika), which targets RNA; (iii) Q-beta replicase (Q-beta R; Gene Trak), which amplifies probes of RNA; (iv) branched-probe technology (bDNA; Chiron), which amplifies DNA signal; and (v) Hybrid amplification (Digene), which is RNA-DNA signal amplification-based test (84,351).

Populations To Be Tested For Chlamydia

Ideally, all sexually active women should be screened for *C. trachomatis*; however, current resources preclude achievement of such a goal. All women suspected of having chlamydial genital tract infection should have specific diagnostic testing (6). This includes women with symptoms, signs, or history of exposure to chlamydia, such as MPC, endometritis, PID, or acute urethritis, or women whose partners have NGU. Stamm (390) proposed a set of diagnostic criteria for common *C. trachomatis* infections in women. These criteria are summarized in Table 5.13. High-risk groups of asymptomatic women should be screened for *C. trachomatis.* This includes women attending family planning clinics, prenatal clinics, abortion clinics, or juvenile detention centers. Women who have specific risk factors associated with chlamydial infections, including adolescent age, having a new sexual partner, having multiple

sexual partners, and signs of cervicitis, should be screened (6). It is suggested that strong consideration be given to screening all unmarried pregnant women and all pregnant women with at least one of the risk categories associated with chlamydial infection, especially adolescents (6). The CDC has established recommendations for prevention and treatment of chlamydial infections. Table 5.14 lists the CDC guidelines for screening and testing women for chlamydial infection. Burstein and colleagues (391) in Baltimore, Maryland, proposed that female adolescents be rescreened at 6-month intervals because of the high rate of recurrence in the 6 months following treatment of chlamydial infection among adolescents.



Associated Findings	Clinical Criteria	Laboratory Criteria	
		Presumptive	Diagnostic
MPC	Mucopurulent cervical discharge; cervical ectopy and edema; friable cervix	Cervical GS >30 PMN/HPF	Positive culture, antigen test or NAA (cervix, first voided urine)
Acute urethral syndrome	Dysuria or frequency in young sexually active women; recent new sexual partner; >7 days of symptoms	Pyuria; no bacteriuria	Positive culture, antigen detection or NAA (cervix, urethra or FVU)
PID	Lower abdominal pain; adnexal and cervical motion tenderness; evidence of mucopurulent cervicitis often present	Cervical GS >30 PMN/HPF; endometritis on endometrial biopsy	Positive culture, antigen detection or NAA (cervix, endometrium, tube, or FVU)
Perihepatitis	Right upper quadrant pain; nausea, vomiting, fever; young sexually active women; evidence of PID	As for MPC and PID	High titer IgM or IgG antibody to *C. trachomatis*

FVU, first voided urine; GS, Gram stain; HPF, high power field; MPC, mucopurulent cervicitis; NAA, nucleic acid amplification; PMN, polymorphonuclear leukocytes.
From Stamm WE. Diagnosis of *Chlamydia trachomatis* genitourinary infections. Ann Intern Med 1988;108:710.

TABLE 5.13. DIAGNOSIS OF COMMON *CHLAMYDIA TRACHOMATIS* INFECTION IN WOMEN

1. Universal screening of adolescents or young adults (<24 yr old) undergoing pelvic examination
2. Annual testing
   A. Women with mucopurulent cervicitis
   B. Sexually active women <20 yr old
   C. 20–24 yr old
      1) Inconsistent use of barrier contraceptives
         or
      2) New partner in past 3 mo
   D. >24 yr old
      1) Inconsistent use of barrier contraceptives
         and
      2) New partner in past 3 mo
3. Screen pregnant women in first trimester
   A. For high-risk women, rescreen in third trimester

From Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47:53–58.

TABLE 5.14. CENTERS FOR DISEASE CONTROL AND PREVENTION RECOMMENDATIONS FOR PREVENTION AND TREATMENT OF CHLAMYDIAL INFECTION IN WOMEN

Selection of a diagnostic test for detection of chlamydial genital infection is dependent on the availability, local expertise, and prevalence of *C. trachomatis* in the test population (6). Because of their high specificity, nucleic acid amplification technologies and cell culture may be most appropriate for screening low-risk

populations. In populations with a moderate-to-high prevalence of chlamydia (greater than 8%), DFA smear, immunoassay, and DNA probes are useful.

THERAPY OF CHLAMYDIAL INFECTIONS

Given the morbidity associated with chlamydial infections, some efforts at control measures are indicated. In the past, such measures required the introduction of chlamydial isolation procedures on a much broader scale than was feasible. The introduction of antigen detection methodology and, more recently, nucleic acid amplification tests has facilitated establishing large-scale screening efforts for chlamydia. The first step was introduction of chlamydial diagnostic techniques for management of genital tract complaints in women. They are at the greatest risk to develop serious complications of chlamydial infection and are epidemiologically crucial in both vertical and horizontal transmission.

It seems appropriate that pregnant women were the first focus of chlamydial control measures. Schachter (19) estimated that each year in the United States, 155,000 infants were exposed to chlamydial infections and more than 100,000 acquired these infections, with approximately 75,000 cases of conjunctivitis and 30,000 cases of pneumonia each year. In addition, these women may be at risk to develop complications of pregnancy (i.e., PROM, preterm delivery) or postpartum endometritis (95,282,283,290,291 and 292).

Three general approaches were used as control measures to prevent chlamydial infection in pregnancy. The first was an effort to reduce the reservoir. The routine use of concomitant tetracycline or doxycycline (as recommended by the CDC) for treatment of gonorrhea addressed removal from the infective pool of approximately 20% to 30% of men and 30% to 50% of women with gonorrhea who had coexistent chlamydial infection. Effective treatment of men with NGU with tetracycline or erythromycin and routine treatment of their sexual contacts also was recommended. Management of mucopurulent endocervicitis in women in the same manner as treatment of NGU in men also helped to reduce the pool.

Specific approaches to preventing perinatal infection with *C. trachomatis* were initiated. Erythromycin ointment was substituted for silver nitrate in ocular prophylaxis for neonates. Silver nitrate is clearly ineffective in preventing chlamydial infections. Topical erythromycin is active against *C. trachomatis*, and clinical studies have shown that it prevents the development of chlamydial conjunctivitis, although it does not prevent respiratory tract infection or pneumonia. Because erythromycin also is effective in preventing gonococcal ophthalmia neonatorum and is less irritating to the eye than the silver nitrate that had been in common use, a routine shift to ocular prophylaxis with erythromycin ointment occurred in the 1980s. However, Hammerschlag et al. (392) cautioned that, compared with silver nitrate, neonatal ocular prophylaxis with either erythromycin or tetracycline ophthalmic ointment did not significantly reduce the incidence of chlamydial conjunctivitis in the offspring of mothers with chlamydial infection. These authors concluded that screening and treatment of pregnant women for chlamydial infection was the better prevention strategy.

Preventing exposure of infants to chlamydia during the birth process involves routine testing of pregnant women for chlamydial infection and treating those found to carry the organism. Although this can be an expensive undertaking (less so with antigen

detection and nucleic acid amplification methods), Schachter and Grossman (18) showed that it can be justified, not only as a public health measure, but also as a cost-effective measure in selected populations. The consistency of attack rates observed in prospective studies allows reasonable certainty in predicting the outcomes of exposure to chlamydia during vaginal deliveries. The prevalence of chlamydial infection in the maternal cervix is the crucial determinant in the incidence of disease in infants. The cost-benefit analysis developed by Schachter and Grossman noted that when the prevalence of chlamydial cervical infection is 5% or less, it cost more to detect and treat infections than it would to treat the resulting diseases in newborns. This analysis may be an underestimate. It was made on the basis of disease in infants, and possible complications of pregnant women were not included because their frequency of occurrence was not known. In addition, antigen detection and nucleic acid amplification technology should lower the cost of screening. When the cervical infection rate is greater than 6%, the costs of treating disease in infants exceeds the costs of identifying and treating pregnant women with cervical chlamydia to prevent perinatal exposure. Because infection rates greater than 5% are commonly reported among pregnant women regardless of race/ethnicity or socioeconomic status, routine screening for chlamydial infections should be initiated for these expectant mothers as an adjunct to perinatal care (2,54).

The treatment of choice to manage chlamydial infection during pregnancy has not been clearly delineated. The CDC recommendations for treatment of chlamydial genital tract infection during pregnancy are provided in Table 5.15. Because doxycycline and the fluoroquinolone ofloxacin are contraindicated for pregnant women, erythromycin base and amoxicillin are the CDC-recommended regimens for treatment of chlamydial infection during pregnancy. At the time when the current CDC guidelines for treatment of chlamydial infection were published, the safety and efficacy of azithromycin in pregnant and lactating women had not been established (54). Thus, azithromycin was suggested as an alternative regimen for pregnant women (54). Other alternatives include erythromycin ethylsuccinate or the option of halving the dose of erythromycin base or ethylsuccinate but doubling the length of therapy for patients not able to tolerate the larger dose of erythromycin (54). Erythromycin estolate is contraindicated in pregnancy because it is associated with drug-induced hepatotoxicity (54). Unlike the situation with nonpregnant women, the CDC suggests repeat testing 3 weeks after completion of the recommended regimens for pregnancy because (a) neither of the regimens is highly efficacious and (b) the frequent side effects of erythromycin impair patient compliance (52).

Recommended regimen for pregnant women
Erythromycin base 500 mg p.o. four times a day for 7 days
or
Amoxicillin 500 mg p.o. three times a day for 7 days
Alternate regimens for pregnant women
Erythromycin base 250 mg p.o. four times a day for 14 days
or
Erythromycin ethylsuccinate 800 mg p.o. four times a day for 7 days
or
Erythromycin ethylsuccinate 400 mg p.o. four times a day for 14 days
or
Azithromycin 1 g p.o. in a single dose

From Centers for Disease Control and Prevention. 2001 guidelines for treatment of sexually transmitted diseases.

TABLE 5.15. CENTERS FOR DISEASE CONTROL AND PREVENTION 2001

RECOMMENDATIONS FOR TREATMENT OF CHLAMYDIAL GENITAL TRACT INFECTIONS DURING PREGNANCY

Several studies have documented the efficacy of erythromycin treatment in eradicating chlamydial infection in pregnant women and preventing vertical transmission of chlamydia to neonates (393,394,395,396,397,398,399,400,401 and 402). Schachter et al. (393) reported that the vertical transmission rate for *C. trachomatis* could be reduced from 50% neonatal infection to 7% with erythromycin treatment for 1 week beginning at 37 weeks' gestation. In prospective randomized trials during pregnancy, erythromycin given in the 2 g/day regimens resulted in cure rates of 84% to 94% (6,321,393). However, as many as 50% of pregnant women develop gastrointestinal side effects that preclude them from completing the course of therapy (6,321,393,394,395,396,397,398,399,400,401 and 402). Subsequently, Crombleholme et al. (403) were the first to demonstrate that amoxicillin is very effective in preventing vertical transmission of *C. trachomatis.* These authors reported that amoxicillin 500 mg three times a day for 7 days eradicated maternal chlamydial cervical infection in 63 (98.4%) of 64 patients, and 37 (95%) of 39 infants had no evidence of chlamydial infection as assessed by culture and serology. In addition, amoxicillin was well tolerated. Subsequent, randomized, prospective trials comparing amoxicillin and erythromycin for treatment of chlamydial infection in pregnancy were reported (394,395 and 396,404). These studies demonstrated treatment success in 85% to 99% of amoxicillin-treated patients compared to 72% to 88% of erythromycin-treated cases. In a meta-analysis of these trials, Turrentine and Newton (397) reported that the relative risk of treatment success was significantly increased in the amoxicillin group (RR, 1.11; 95% CI, 1.05–1.18; $p < 0.01$). Moreover, gastrointestinal side effects in the amoxicillin group ranged from 6% to 16% compared to 25% to 49% with erythromycin. The meta-analysis demonstrated a 70% reduction in gastrointestinal side effects (RR, 0.29; 95% CI, 0.20–0.42; $p < 0.01$) (397). Because of similar or better efficacy and significantly improved tolerance, amoxicillin may be the treatment of choice for antenatal *C. trachomatis* infection (397). Alger and Lovchik (398) compared clindamycin to erythromycin during pregnancy and noted that both clindamycin and erythromycin were effective, with cure rates of 92.7% and 83.8%, respectively.

Azithromycin for use in pregnancy is recommended by the CDC as an alternative for treatment of chlamydial infection during pregnancy. Only a limited number of studies have addressed the use of azithromycin for treatment of chlamydial infection during pregnancy (399,400 and 401). In an initial small randomized study, Bush and Rosa (399) compared azithromycin 1 g orally as a single dose with erythromycin 500 mg orally four times a day for 7 days. Cure rates were similar (100% and 93% for azithromycin and erythromycin, respectively), but 5 (33%) of 15 patients were intolerant to the 500-mg erythromycin dose compared to none in the azithromycin group ($p < 0.025$). Edwards et al. (400) reported that azithromycin 1 g orally as a single dose had a significantly higher cure rate than erythromycin, with 4 (6.2%) versus 18 (27.7%) treatment failures, respectively. Gastrointestinal side effects were noted in 42 (65.5%) women taking erythromycin compared to only 12 (19.4%) women taking azithromycin ($p < 0.002$) (400). Adair and coworkers (401) also reported that pregnant women treated with azithromycin had significantly fewer gastrointestinal side effects than women treated with erythromycin (11.9% vs.

58.1%; *p* £ 0.01). However, they noted similar treatment efficacy for azithromycin and erythromycin (88.1% vs. 93%). Wehbeh et al. (402) noted not only a significant reduction in GI side effects with azithromycin compared to erythromycin (7.4% vs. 38.8%; *p* = 0.02), but also a significant improvement in cure rates (95.5% vs. 78.9%; p = 0.018).

The CDC-recommended treatment for chlamydial infection of the lower genital tract in nonpregnant patients is given in Table 5.4. Either doxycycline 100 mg orally twice a day for 7 days or azithromycin 1 g orally as a single dose are the suggested treatments of choice. In a controlled trial, Martin et al. (405) demonstrated that a single 1-g dose of azithromycin was as effective as 7 days of doxycycline (96% vs. 97%) and as well tolerated. Magid et al. (406) compared the health outcomes, costs, and incremental cost-effectiveness of doxycycline therapy for 7 days versus single-dose therapy with azithromycin. Although the single 1-g dose of azithromycin is approximately 3.5 times more expensive than 7 days of doxycycline therapy, these authors concluded that azithromycin single-dose therapy is the most cost-effective approach. In their analysis, azithromycin caused fewer major and minor sequelae of chlamydial infection. The fluoroquinolone ofloxacin and erythromycin base of erythromycin ethylsuccinate are alternative regimens. Ciprofloxacin has been demonstrated to be ineffective against *C. trachomatis* due to relapsing infection (407). Additional drugs that have demonstrated *in vitro* activity against *C. trachomatis* include sulfamethoxazole-trimethoprim, rifampin, and clindamycin (408, 409). Single-dose regimens of penicillin G or ampicillin are ineffective.

As discussed in Chapter 14, an antichlamydial agent, usually doxycycline or clindamycin in the parenteral regimens and doxycycline or ofloxacin in the oral regimens (54), is part of a combination therapy approach to treatment of acute PID. Clindamycin in clinical trials has been shown to be an effective agent against *C. trachomatis* in patients with PID (109).

Chlamydial inclusion conjunctivitis usually is treated with tetracycline or erythromycin eye drops. For chlamydial pneumonia, systemic erythromycin therapy is advocated. General consensus suggests that chlamydial conjunctivitis of the newborn also should be treated with systemic erythromycin, because of high failure rates observed with topical treatment. A 2-week course of erythromycin at a dose of 40 mg/kg/day is recommended. Systemic therapy also will eradicate nasopharyngeal colonization and prevent pneumonia secondary to chlamydia.

PREVENTION

The Institute of Medicine has endorsed as a national public health priority the nationwide implementation of screening programs for *C. trachomatis* among young, sexually active women (410). The CDC has actively promoted such a priority (2,54). Stamm (411) has suggested that until an effective vaccine for *C. trachomatis* infection becomes available, successful control of sexually transmitted chlamydial infection must rely on broad-based screening programs. The rationale for such an approach is based on a number of findings, including (i) the high prevalence of chlamydial infections, especially among adolescents and young adults; (ii) chlamydial infections have a greater distribution than other bacterial STDs among all socioeconomic, racial, and ethnic groups; (iii) most chlamydial infections in women are asymptomatic; (iv) chlamydial infections can persist for long periods of time (months) and thus provide a large window of opportunity for transmission to occur;

(v) chlamydial infections, if left untreated, are associated with significant adverse sequelae, such as PID, tubal infertility, ectopic pregnancy, and poor pregnancy outcome; and (vi) chlamydial infections and their complications are responsible for an estimated $2.4 billion in health care costs annually (6,364,410).

Because the majority of chlamydial infections in women are asymptomatic, effective control of these infections requires periodic screening of individuals at risk for *C. trachomatis* infection (6). Concerns over the cost of establishing widespread screening for *C. trachomatis* led to an attempt at identifying populations at increased risk for chlamydial infection (6). Initially, the focus was universal screening of patients attending clinics with high prevalence rates of *C. trachomatis,* such as STD clinics, urban family planning clinics, inner city prenatal clinics, and juvenile detention centers. However, this approach failed to address the large number of asymptomatically infected women not attending such sites (6).

The focus of prevention then switched to developing selective screening criteria for identifying which persons attending health care sites should be screened for chlamydial infection. As discussed previously in the section on Epidemiology and Transmission, a number of patient characteristics are predictive of chlamydial infection (1,6,8,61,63,64,71,78,85,99,100,101,102,103 and 104,106,107). Briefly, these factors include young age (less than 21 years), presence of MPC, partners with nongonococcal urethritis, new sexual partners, multiple sexual partners, and either lack of contraception or nonbarrier methods of contraception. Studies from the northwest United States (4), Family Planning Clinics in Wisconsin (56), and adolescent clinics (57) and studies of military recruits (412) have demonstrated the effectiveness of selective screening in decreasing the prevalence of *C. trachomatis* infection in women. As an example of the significant impact such screening programs can have, the CDC reported that the prevalence of chlamydial infections in women declined by more than 50% (from 10%–12% to 4%–5%) from the late 1980s to 1995 once extensive screening programs were instituted in family planning clinics and STD clinics (4).

Of substantial public health interest has been the demonstration that screening programs for *C. trachomatis* can reduce the incidence of complications of chlamydial infection (141,413). Scholes et al.(141) reported that, in a prospective randomized study at a health maintenance organization, women who met selective screening criteria and were randomized to the group tested for chlamydial cervical infection had a significant decrease in the incidence of symptomatic PID at the 1-year followup (OR, 0.44; 95% CI, 0.20–0.90). Egger et al. (413) reported that declining rates of genital chlamydial infection in Uppsala County, Sweden, were associated with a decrease in the rate of ectopic pregnancy.

Several analyses of the cost-effectiveness of chlamydial screening programs have been reported (412,414,415,416 and 417). In general, these studies suggested that universal screening is preferred in clinical settings where the prevalence of chlamydial infection is above the 3% to 7% rate. On the other hand, selective screening is the more cost-effective approach for populations with a prevalence of chlamydial infection below the 3% to 7% range (6).

The CDC suggested criteria that could be used to help identify women who should be tested for chlamydia, especially in low-prevalence populations (Table 5.14). Richey et al. (418) demonstrated that prevention programs targeting adolescents

should include repeat testing of all women with prior chlamydial infection, irrespective of their age. Burstein et al. (391) suggested that adolescents be screened at 6-month intervals because of the high rate of acquisition of new chlamydial infection in this population.

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6

HERPES SIMPLEX VIRUS INFECTION

In this heavily revised chapter, we have added clinically important information on developing our understanding of the natural history of herpes simplex virus (HSV) infections. New diagnostic techniques and new treatments have been developed. In addition, our understanding of acquisition of perinatal HSV infection has been expanded.

Herpes simplex virus belongs to the Herpesviridae family, which is a group of double-stranded DNA viruses. Well-recognized are HSV type 1 (HSV-1) and type 2 (HSV-2). Other members of this family include the varicella-zoster virus (VZV). Infections caused by these viruses enter through mucus membranes or epidermis, producing typical clinical vesicular lesions. These infections have a neurotropism with sensory neural involvement and latency within the dorsal root ganglion. After primary infection, HSV replicates at the mucous membrane or epidermal portal of entry and then travels through the axon to the dorsal root ganglion, where latency persists throughout life. What triggers the active replication stage to recurrent lesion in the healthy adult is not entirely clear. Although immunosuppression certainly is a risk factor, some healthy adults never have recurrences, whereas others have frequent and severe episodes (1).

Genital herpes is a sexually transmitted disease caused by HSV-1 and HSV-2. Herpes simplex virus contains an inner core of double-stranded DNA surrounded by a glycoprotein envelope. The two types of HSV are distinguished by biochemical, immunologic, and serologic methods. Infections by HSV-2 are found primarily in the genital area, but approximately 15% of primary genital herpes infections are caused by HSV-1. The use of restrictive endonuclease cleavage of the HSV DNA has

uncovered multiple specific strains of HSV-1 and HSV-2, rather than only the two types.

EPIDEMIOLOGY

Recognition of the increasing prevalence of herpesvirus infections developed in the 1970s. Estimates from the Centers for Disease Control and Prevention (CDC) demonstrated that from 1966 to 1997, there was a ninefold increase to over 200,000 physician visits for genital herpes (2). It is estimated that 500,000 new cases of genital HSV infection occur annually in the United States. Overall, 5% to 10% of the population has a history of systematic genital HSV-2 infection. A larger percentage of the population has type-specific HSV-2 antibodies (to glycoprotein G) and thus has unequivocal serologic evidence of previous infection with HSV-2, yet these individuals have never had a recognized symptomatic infection. Seroprevalence data showed that for the period from 1988 to 1994, the overall seroprevalence for HSV-2 infection was 21.9% and among females was 25.6% (3). Seropositivity rates varied by racial and ethnic group. Among white females, the seropositivity rate was 20.2%. Among Mexican-American females, it was 25.7%, whereas among black females it was 55.1%. HSV-2 seroprevalence also increases with age. For example, among white females, seroprevalence rises from approximately 5% in the teenage years to 20% by age 30 years. In comparison, among black females, seroprevalence rises from about 10% in teenagers to approximately 55% by age 30 years and then to nearly 80% by age 60 years. Comparing seroprevalence from 1988 to 1994 with that from 1976 to 1980, Fleming and colleagues (3) reported an overall seroprevalence increase of about 30% (from 16% in the earlier period to 20.8% in the later period overall). Thus, infection is now detectable in about one fifth of persons over age 12 years. On the basis of clinical history, serology, and HSV typing, we now recognize that there are three types of HSV genital infections: primary infection, recurrent infection, and nonprimary first episode. Primary infection is initial infection with either HSV-1 or HSV-2, without prior exposure (i.e., antibodies to either). Recurrent infection is reactivation of latent virus, not a reinfection. Nonprimary first episode is a first episode (either clinical or subclinical) with HSV-1 or HSV-2 in a patient with prior exposure to the other serotype (Box 1).

Box 1

Genital Herpes Syndromes

- Primary infection: initial infection with either herpes simplex virus type 1 or 2, without prior exposure (i.e., antibodies) to either
- Recurrent infection: reactivation of latent virus, not a reinfection
- Nonprimary first episode: first clinical episode with herpes simplex virus type 1 or 2 in a patient with prior exposure to the other viral serotype

Traditionally, it has been taught that primary infection lasts for an average of 20 to 21 days, progressing through vesicular, ulcerative, and crusting stages. These primary infections generally have been thought to be accompanied by fever, malaise, adenopathy, and dysuria. The infections may be complicated by distal site inoculation (whitlow), asymptomatic meningitis, and urinary retention. Recent

evidence has shown that the vast majority of HSV-2 seropositive adults have no reported episodes clinically diagnosed as genital herpes infection (3). In addition, Hensleigh and colleagues (4) reported that even most “severe” first episodes are not true primary infections. Further, it has been taught that recurrent infections last 2 to 7 days, with active viral shedding for 1 to 5 days. Recurrent lesions have been thought usually to be preceded by a recognizable syndrome in about 70% of patients and not accompanied by constitutional symptoms. Patients with a past history of genital HSV may asymptomatically shed the virus from the genital tract on about 1% of days, and such asymptomatic shedding lasts about 1 to 5 days. Again, Hensleigh et al. (4) reported that many “severe” first clinically recognized episodes are actually recurrent infections when HSV typing and antibody testing are performed. Nonprimary first episodes traditionally have been taught to be similar to recurrent episodes clinically. Again, however, Hensleigh et al. (4) reported that some “severe” first episodes are actually nonprimary first episodes. Thus, although there are general distinguishing features between true primary and recurrent genital herpes infection, as shown in Table 6.1, there are many exceptions to these characteristics, and correct classification requires clinical correlation with viral isolation and type-specific serology (4) (Box 2).

Box 2

Classification of Genital Herpes Simplex Virus Syndromes

Although there are some general distinguishing features among the three syndromes, correct classification requires clinical correlation with viral isolation and type-specific serology.

Feature	True Primary	Recurrent
Incubation period	2–10 days	
Prodrome		1–2 days
Fever	+	
Regional lymphadenopathy	+	
Malaise	+	
Duration of genital symptoms (mean)	~15 days	~7 days
Duration of viral shedding (mean)	~12 days	~5 days
Number of lesions	Greater	Fewer
Cervical lesions	Common	Uncommon

TABLE 6.1. TRADITIONALLY RECOGNIZED CHARACTERISTICS OF CLINICALLY EVIDENT TRUE PRIMARY AND RECURRENT GENITAL HERPES INFECTION

As previously noted, less than 10% of individuals seropositive for HSV-2 gave a history of clinically evident disease. However, these data were derived from largely retrospective databases. In a recent prospective study defining the natural history of newly acquired symptomatic and asymptomatic HSV infection in sexually active

adults, data were quite different. Of 155 newly acquired HSV-2 infections, 37% were associated with clinically symptomatic disease (5). Seventy-five percent of these cases were associated with lesions of the skin and mucosa of the genital tract, but it is noteworthy that presentation was not immediately suggestive of herpes in 13%. In particular, these patients had symptoms suggestive of cystitis, meningitis, urethritis, and cervicitis. In addition, clinical disease subsequently developed in 15% of persons with asymptomatic seroconversion on later follow-up. Overall, this investigation of 2,393 sexually active HSV-2 seronegative persons indicated rates of new HSV-1 and HSV-2 infection of 1.6 and 5.1 cases per 100 person-years, respectively. At the time of initial presentation of HSV-2 infections, 82% (47/57) of symptomatic cases were correctly diagnosed initially. It also was noted that women were more likely than men to acquire HSV-2 infection ($p < 0.01$) and to have symptomatic infection. Previous HSV-1 infection did not reduce the rate of HSV-2 infection, but it did increase the likelihood of symptomatic seroconversion. The authors noted that of 19 new HSV-1 cases, 12 were symptomatic. The rates of symptomatic genital HSV-1 infection and oral HSV-1 infection were the same at 0.5 cases per 100 person-years. Thus, with careful evaluation, nearly 40% of newly acquired HSV-2 infections and nearly two thirds of HSV-1 infections are symptomatic from this prospective study. Among sexually active adults, new genital HSV-1 infections are as common as new orogenital HSV-1 infections (5).

It must be emphasized that most antibody tests available through commercial laboratories show cross-reactivity between antibodies to HSV-1 and HSV-2 and cannot be used to determine prevalence. However, a new commercial glycoprotein G-based enzyme immunoassay recently has been approved and released by Gull Laboratories (Salt Lake City, UT). This enzyme immunoassay was compared with estern blot (used previously in research laboratories) for detection of HSV-1 or HSV-2 antibodies in 193 serum samples in a premarket evaluation. The new Gull Laboratories assay showed sensitivity for HSV-1 of 95% and specificity of 96%. The sensitivity for HSV-2 was 98% and corresponding specificity was 97%. Accordingly, this new commercially available assay should simplify detection of antibody status when testing is clinically indicated (6). Herpes simplex virus may be acquired from an asymptomatic sexual partner. The vast majority (70% to 85%) of individuals with HSV-2 antibodies do not have symptoms. Koutsky and colleagues (7) in Seattle, Washington, recently demonstrated that only 22% (82/372) of women with serologic or virologic evidence of HSV infection had symptoms. Additionally, 4% (14 women) had viral shedding without symptoms, 16% (60) previously had symptomatic episodes, and 58% (216) had antibodies to HSV-2 with neither viral shedding nor a history of clinical episodes (7).

In surveys of adult females, HSV has been isolated from the genitalia of 0.02% to 4% of women. In high-risk populations, such as women attending a venereal disease clinic, the rate is at the higher end of the range. Among pregnant women, surveys have found positive cultures in 0.01% to 4% of asymptomatic women. Of all patients with positive cultures, those without symptoms have been reported to account for between approximately one and two thirds (8,9). Pregnancy probably does not lead to an increase in frequency or severity of genital herpes infections.

Some researchers have reported that maternal infection has adverse effects in early pregnancy, reporting a threefold increase in abortion. Infants with neonatal herpes infections have a high rate of prematurity, but the premature infant may simply be a more susceptible host. Prematurity is not increased in women with recurrent herpes

infections. Comparing neonates of 94 mothers who seroconverted to HSV-1 or HSV-2 during pregnancy to those of 6,009 without seroconversion, Brown and colleagues (10) found no observed differences in mean birthweight, gestational age at birth, likelihood of intrauterine growth restriction, stillbirth, or neonatal death. Thus, acquisition of HSV infection during pregnancy usually is devoid of sequelae. The major problem is perinatal neonatal herpes infection. Transplacental infection of the fetus resulting in congenital infection is a rare sequela to maternal infection. Only a few documented cases have been reported. In a report of 13 such cases, Hutto et al. (11) reported devastating effects, with death in 31% and neurologic sequelae in nearly all survivors.

The important perinatal problem is neonatal herpes infection. Exact estimates of its frequency are subject to error, because up to 50% of infants with culture-proved, fatal disease may not show typical lesions on the skin or mucous membranes. Thus, the viral infection may not be recognized. In addition, viral laboratories have not been widely available, and recent treatment recommendations probably have decreased the incidence of neonatal disease. It is estimated that 700 to 1,000 cases of neonatal herpes occur annually in the United States, for an incidence of 1 in 3,500 to 1 in 5,000.

Neonatal herpes may be acquired perinatally from an infected lower maternal genital tract, most commonly during vaginal delivery. Other cases have occurred in newborns delivered by cesarean birth, most often when performed a number of hours after labor has begun or after the membranes have ruptured. Still other neonates may acquire the virus nosocomially. The estimated risk of neonatal infection has been markedly revised and will be discussed in detail later (12).

CLINICAL PRESENTATION

As noted earlier, the clinical manifestations of genital HSV occur as three distinct syndromes. The limitations of clinical diagnosis alone have been noted. In general, true primary HSV is associated with more marked local symptoms, i.e., multiple painful lesions progress from vesicles to an ulcerative state, inguinal adenopathy, and systemic effects, such as fever, malaise, myalgias, headaches, and nausea. In immunocompetent adults, the disease usually is self-limited. However, a small percentage (approximately 4%) of those with primary genital herpes will have accompanying viral meningitis. First-episode nonprimary genital herpes usually is similar to recurrent genital herpes, but it may be variable. Recurrent disease occurs more frequently after primary HSV-2 infection than after HSV-1. The appearance of typical lesions is preceded by local prodromal symptoms of paresthesias, itching, or pain. The prodrome usually lasts about 2 days. Often, mild local symptoms occur and last about half as long as those of primary first-episode HSV infection. Usually a few lesions occur, and systemic manifestations are absent. In addition, the duration of viral shedding is shorter (usually 3 to 5 days), and the likelihood of concomitant cervical HSV shedding is less than with primary disease. Nevertheless, recurrent episodes (as confirmed by viral isolation of antibody testing) may present with severe symptomatology. Clinically detectable recurrences occur variably, but about 50% of patients will have recurrent disease within 6 months. Further, the likelihood of recurrence depends on the serotype of HSV. Recurrences are milder, with fewer lesions, fewer constitutional symptoms, and a shorter course (usually 7 to 10 days) (Table 6.1). Corey and Spear (13,14) noted that within 12 months of a first episode, 80% of patients with HSV-2 infection had a recurrence (mean 4), whereas 55% with

HSV-1 infection had a recurrence (mean less than 1).

DIAGNOSIS

Although histologic examination of vulvar lesions reveals characteristic findings (Fig. 6.1), biopsy is rarely used for diagnosis of genital lesions. Until recently, the best diagnostic test to confirm the presence of herpesvirus infection was viral culture. For clinical use, it is fortunate that this virus grows rapidly; most positive cultures are identifiable at 48 to 72 hours. This virus is hearty and can be transported on ice, when necessary. Overall, for a single herpes culture, there is a recognized false-negative rate of perhaps 5% to 30%. Several clinical features influence the likelihood of a positive culture. For example, cultures are more likely to be positive in first episodes than in recurrent episodes. In patients with suspected recurrent genital herpes, Lafferty et al. (15) noted that the likelihood of a positive viral culture was higher in patients with vesicles or pustules and lower in patients with ulcerative and crusted lesions. Further, positive cultures were more likely early in the course of a lesion (within 72 hours) than later. Techniques are now available to accelerate detection of HSV in culture. These techniques usually utilize specific monoclonal antibodies in immunofluorescence or enzyme immunoassays. Many of these tests show good sensitivity and specificity (16).

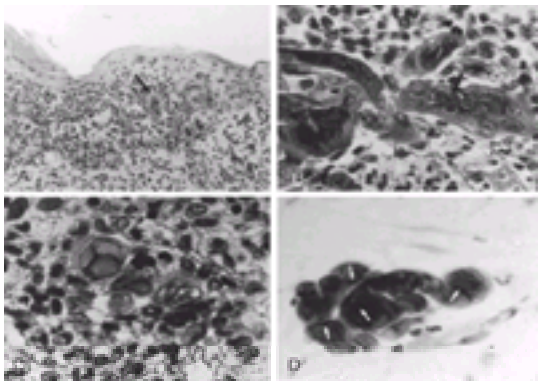


FIGURE 6.1. Characteristic histologic changes seen in herpes simplex virus infection of the vulva. **(A)** Necrosis of the epidermis and dermis, with acute inflammation and nuclear debris *(left),* viable mucosal keratinocytes *(right),* and multinucleated giant cells *(center; arrow)* (hematoxylin-eosin, original magnification ×90). **(B)** Multinucleated cells with Cowdry type A intranuclear viral inclusions *(arrow)* (hematoxylin-eosin, original magnification ×220). **(C)** Nuclear molding (the contours of adjacent nuclei conform to one another) with a ground-glass chromatin pattern *(arrow)* in an enlarged, multinucleated cell (hematoxylin-eosin, original magnification ×480). **(D)** Vaginal smear shows margination by nuclear chromatin *(arrows)* (Papanicolaou stain, original magnification ×550). (From Brennick J, Duncan L. Images in clinical medicine. *N Engl Med* 1994;329:1783, with permission.)

In addition to documenting that most women with unequivocal serologic evidence of infection are asymptomatic, Koutsky et al. (7) noted that some women (9% [6/66])

with culture-confirmed HSV infection present with atypical lesions, such as fissures, furuncles, excoriations, or nonspecific vulvar erythema.

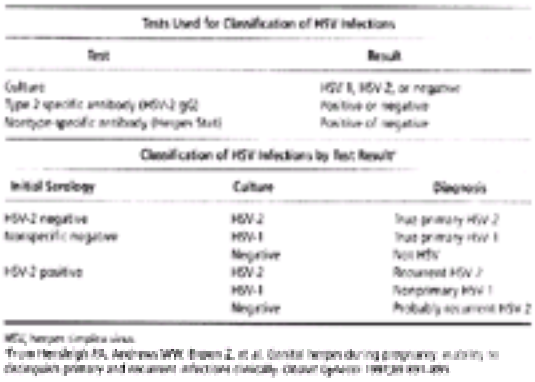
Although HSV infection may be suggested by rather typical changes seen in Papanicolaou smear (intranuclear inclusions and multinucleated giant cells), the sensitivity of this test is inadequate at about 50% (i.e., about 50% false-negative rate).

The monoclonal antibody and enzyme-linked immunosorbent assay tests have modest sensitivity.

The laboratory diagnosis of HSV infections has been revolutionized by advances in molecular biology and serologic techniques. The most sensitive diagnostic technique is the polymerase chain reaction (PCR) (17,18 and 19). In preliminary results, this technique was able to detect HSV DNA in 12 pregnant women with genital lesions from whom HSV was isolated in culture (eight with HSV-2 and four with HSV-1) and from 11 women with asymptomatic shedding at delivery. None of 11 samples from women with HSV-2 antibodies but with negative cultures was positive by PCR. Thus, PCR had 100% sensitivity and 100% specificity compared with viral culture (17). Another study showed that with PCR, HSV DNA was detected in 38 genital specimens, 32 of which were positive by culture. Another specimen was positive by culture but negative by PCR (18). These data demonstrate that PCR is a rapid and sensitive diagnostic technique for HSV detection from clinical specimens. It is now widely available, but quality control may vary among laboratories.

Neonatal herpes infection may be limited to the skin or may have systemic involvement either with or without cutaneous involvement. Typically, clinical disease begins at the end of the first week of life or later. Because findings depend on the organ system involved, the presentation may include skin lesions, cough, cyanosis, tachypnea, dyspnea, jaundice, seizures, or disseminated intravascular coagulopathy. In infants at risk for, or suspected of having, neonatal herpes, the only reliable diagnostic test is viral culture. One cannot rely on clinical examination or cytologic findings. A few infants have been recognized with congenital (transplacental) herpes infection. Manifestations usually are apparent within the first 7 days. Transplacental infection presumably results from maternal viremia, which occurs only with primary maternal infection.

Use of type-specific serology and viral isolation in correctly categorizing genital HSV episodes was discussed earlier. One algorithm uses viral isolation and typing, the type 2 specific antibody, and a nontype-specific antibody (Herpes Stat) (4). Interpretation of these results is given in Table 6.2.



Tests Used for Classification of HSV Infections

Test	Result
Culture	HSV-1, HSV-2, or negative
Type 2 specific antibody (HSV-2 gG)	Positive or negative
Nontype-specific antibody (Hengen Stat)	Positive or negative

Classification of HSV Infections by Test Result[a]

Initial Serology	Culture	Diagnosis
HSV-2 negative	HSV-2	True primary HSV-2
Nonspecific negative	HSV-1	True primary HSV-1
	Negative	Not HSV
HSV-2 positive	HSV-2	Recurrent HSV-2
	HSV-1	Nonprimary HSV-1
	Negative	Probably recurrent HSV-2

HSV, herpes simplex virus.
[a]From Hershgold EJ, Andrews WW, Bowes Z, et al. Genital herpes during pregnancy: [illegible] to distinguish primary and recurrent infections clinically. Obstet Gynecol 1981;58:162.

TABLE 6.2. CLASSIFICATION OF GENITAL HERPES SIMPLEX VIRUS INFECTIONS USING VIRAL ISOLATION AND ANTIBODY TESTING

TREATMENT

Acyclovir

In the early 1980s, the first effective antiviral chemotherapeutic agent for genital herpes became available. Acyclovir (Zovirax) interferes selectively with viral thymidine kinase. Acyclovir is concentrated in HSV-infected cells and is converted to the active derivative acyclovir triphosphate. Acyclovir is not concentrated in uninfected cells. The active form of the drug is a competitive inhibitor of viral DNA polymerase and is a DNA chain terminator. Thus, its mechanism of action is inhibition of viral DNA synthesis. It has a high margin of safety in view of its selectivity for HSV-infected cells.

Acyclovir is available in several forms for use in genital herpes: a topical 5% ointment in a polyethylene glycol base, a powder for intravenous use, an oral capsule, and an oral suspension. With availability of other acyclovir preparations, there are few, if any, situations where topical acyclovir is preferred.

Intravenous acyclovir sodium is indicated for severe genital herpes (5 mg/kg every 8 hours for 5 days). It was evaluated in a double-blind, placebo-controlled trial of 30 patients with primary genital herpes. In patients given intravenous acyclovir, there was a significant reduction in median healing time, duration of vesicles, duration of symptoms, and duration of viral shedding.

Oral acyclovir capsules are indicated for three circumstances: (i) treatment of primary genital herpes; (ii) treatment of severe recurrences; and (iii) suppression of severe frequent recurrences. The oral preparation offers the advantage of convenience and ease of administration. In a double-blind study of 48 adults with first-episode genital herpes infection, Bryson and colleagues (20) found that oral acyclovir (200 mg, five times a day for 10 days) significantly reduced duration of virus shedding (in women, 4.9 vs. 14.7 days), time to healing (in females, 10 vs. 16.2 days), occurrence of new lesions after 48 hours (in females, 0/16 vs. 8/15), and duration and severity of symptomatology. No toxicity was seen, but recurrence rates

were similar (20).

For some patients with *severe* recurrent episodes, oral acyclovir (200 mg, five times a day for 5 days) leads to a significant decrease in mean time to healing of 1 to 1.5 days compared with placebo (21). These effects are more pronounced when oral acyclovir use is self-initiated by the patient during the first signs of recurrence. An alternative to episodic acyclovir in patients with either severe or mild *infrequent* recurrences is supportive therapy, described later.

For treatment, use of acyclovir 400 mg orally three times a day is as effective and more convenient than the regimen of 200 mg five times daily recommended in the package insert. The use of oral acyclovir to prevent recurrences in patients with frequent episodes (approximately six per year) has been evaluated extensively. In double-blind, placebo-controlled trials, early results have shown that oral acyclovir (either 200 mg three times a day or 400 mg twice a day) daily for up to 6 months significantly decreased recurrences (22,23). Douglas and colleagues (23) noted that in a 4-month trial, 65% of patients taking acyclovir twice a day had no recurrences compared with only 6% of patients taking placebo ($p < 0.001$). However, once oral acyclovir was stopped, there was no influence on subsequent rates of recurrence.

Data reported later regarding suppressive use of oral acyclovir (400 mg twice a day vs. placebo) demonstrated continued efficacy and safety when used for up to 5 years (24,25 and 26). In 1993, Goldberg et al. (27) reported on 389 of 430 patients who began the fifth year of suppressive acyclovir (most at 400 mg twice a day). After a dramatic drop in recurrence rate in the first year, there was a gradual and continued further drop in the ensuing years, but it is not known whether this further decline was due to the drug or the natural history of genital herpes. More than 20% of patients continuing suppressive therapy for 5 years remained recurrence free for the entire period, and 86% to 90% were recurrence free for any 3-month quarter. The mean number of recurrences decreased from 1.7 in the first year to 0.8 in the fifth year. This is impressive, as the mean number initially exceeded 12 per year. There also was a decrease in the number of false prodromes. Only 3% of patients required a higher dose to control recurrences, with 14 of 16 such patients noting a satisfactory response to the higher dose. The safety of long-term suppression was excellent, with a decrease in reported adverse effects over the 5-year period (27).

It has been reassuring that long-term use of suppressive acyclovir (up to 6 years) has not been associated with emerging resistance in immunocompetent patients. Of 239 individuals who stopped acyclovir after 6 years, 86% had at least one recurrence. Herpes isolates from these patients showed a mean sensitivity to acyclovir of 0.79 µg/mL. Only 3.5% were resistant (x3 µg/mL). These values were comparable to background rates. Limited data from 13 patients showed no trend toward resistance in paired pretherapy and posttherapy isolates (28).

The CDC and others currently recommend stopping suppressive acyclovir after 1 year to reassess the patient's condition, because some patients will observe a marked decrease in frequency as part of the natural history of their infection (26,29). However, many patients are aware of the longer-term safety and efficacy data and are reluctant to discontinue suppressive acyclovir after just 1 year. With appropriate counseling, continuing suppressive doses beyond 1 year (without insisting on stopping) seem reasonable. The usual dose for suppression is 400 mg twice a day, but the dose may be titrated from 200 mg twice a day to 200 mg five times a day

(29). Although the 5-year data support continuous use, this seems inappropriate for most patients with genital herpes. Asymptomatic shedding of virus can continue despite decreases in clinically evident recurrences while the patient is undergoing suppressive acyclovir therapy. Thus, the possibility of sexual transmission persists.

Valacyclovir And Famciclovir

Since the last edition of this text, two new preparations have become commercially available. These new oral nucleoside analogue antiviral agents are available for treating both HSV and VZV infection. In addition to acyclovir, the new drugs are valacyclovir (Valtrex), which is the valine ester pro drug of acyclovir; and famciclovir (Famvir), which is the pro drug of penciclovir. The new agents, as well as acyclovir, inhibit actively replicating virus by interfering with the viral DNA synthesis. This interference is through inhibition of thymidine kinase, an enzyme essential for DNA synthesis. None of these drugs has any effect on latency of HSV or VZV. Acyclovir and penciclovir have similar *in vitro* activities against both HSV and VZV, but the advantage of valacyclovir and famciclovir is that they have better absorption and longer half-lives with oral administration. The CDC has recommended these two drugs as well as acyclovir for use as treatment for either first-episode or episodic recurrent herpes or for suppression for individuals with more than six recurrences per year (26). The CDC recommends reevaluating after 1 year those patients on suppressive therapy with any of these regimens. In addition, the 1998 CDC guidelines for treatment of sexually transmitted diseases do not recommend use of famciclovir or valacyclovir for more than 1 year, presumably because long-term data are not available. Regimens for treatment of genital herpes are summarized in Table 6.3.

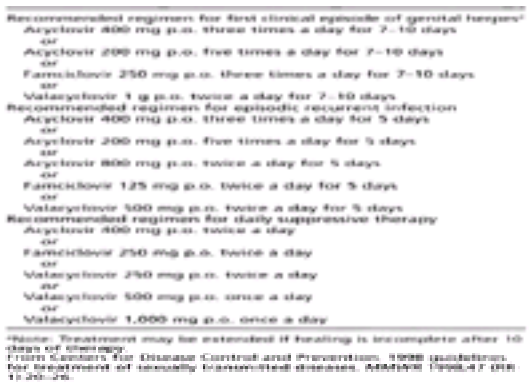

Recommended regimen for first clinical episode of genital herpes[a]
Acyclovir 400 mg p.o. three times a day for 7–10 days
or
Acyclovir 200 mg p.o. five times a day for 7–10 days
or
Famciclovir 250 mg p.o. three times a day for 7–10 days
or
Valacyclovir 1 g p.o. twice a day for 7–10 days
Recommended regimen for episodic recurrent infection
Acyclovir 400 mg p.o. three times a day for 5 days
or
Acyclovir 200 mg p.o. five times a day for 5 days
or
Acyclovir 800 mg p.o. twice a day for 5 days
or
Famciclovir 125 mg p.o. twice a day for 5 days
or
Valacyclovir 500 mg p.o. twice a day for 5 days
Recommended regimen for daily suppressive therapy
Acyclovir 400 mg p.o. twice a day
or
Famciclovir 250 mg p.o. twice a day
or
Valacyclovir 250 mg p.o. twice a day
or
Valacyclovir 500 mg p.o. once a day
or
Valacyclovir 1,000 mg p.o. once a day
[a]Note: Treatment may be extended if healing is incomplete after 10 days of therapy.
From Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47 (RR 1):21–76.

TABLE 6.3. CENTERS FOR DISEASE CONTROL AND PREVENTION REGIMENS FOR GENITAL HERPES

Valacyclovir 500 mg once a day appears less effective than other valacyclovir dosing regimens in patients who have very frequent recurrences (more than ten episodes per year). Few comparative studies of valacyclovir and famciclovir with acyclovir have been conducted. The results of these studies suggest that valacyclovir and famciclovir are comparable to acyclovir in clinical outcome. However, valacyclovir and famciclovir may provide increased ease in administration, which is an important

consideration for prolonged treatment.

Although the CDC recommends five different regimens for daily suppressive therapy (Table 6.3), other regimens, such as oral famciclovir 125 mg or 250 mg three times daily, are available (30). Physicians and patients have multiple choices, including variables of cost, frequency of dosing, and efficacy. Because these regimens are intended for use over months to years, the patient should be involved in the decision making. For example, some patients may be satisfied with a reduction to one to two recurrences per year, and this level of recurrence may be accomplished in some patients with once-daily suppression (7). As noted by Engel (1), a dose-response relationship exists between and among all regimens, and there is a maximum threshold above which additional therapy provides no additional benefit. The therapeutic goal is to establish an optimal effective and affordable dose. Table 6.4 provides a summary of the characteristics of four different regimens for long-term suppression of genital herpes. Whichever regimen is selected, patients should be informed that they may shed infectious virus asymptomatically while receiving any of these regimens; accordingly, patients should be counseled, inform their sexual partners, and use appropriate preventative measures.

			Efficacy[b]	
Drug	Suppressive Dose	Cost per Year[a]	Study Patients Recurrence Free at 1 Year	Median No. of Recurrences per Year[c]
Famciclovir	250 mg twice daily	$2,321	72%	1
Acyclovir	400 mg twice daily	$1,387	48%	1.25
Valacyclovir	500 mg once daily	$1,055	40%	
	1,000 mg once daily	$1,329	48%	

[a]Data are from the *Hospital Formulary Pricing Guide*, July 1998, MediSpan Inc, Indianapolis, IN. The cost is average wholesale price. The cost of acyclovir is based on the generic product.
[b]Efficacy data from Diaz-Mitoma F, Sibbald RG, Shafran SD, et al., for the Collaborative Famciclovir Genital Herpes Research Group. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. JAMA 1998;280:887–892.
[c]Recurrences occurred while patients were receiving suppressive therapy.
Adapted from Engel JP. Long-term suppression of genital herpes. JAMA 1998;280:1528–1529, with permission.

TABLE 6.4. CHARACTERISTICS OF SOME REGIMENS USED FOR SUPPRESSION OF GENITAL HERPES INFECTIONS

Vaccination

An effective HSV vaccine is considered important to prevent, or more likely modify, primary infection. Vaccine given to those with recurrent infections may ameliorate these recurrences. If given to pregnant or reproductive age women, it is possible that the vaccine may prevent or modify neonatal infection. In 1989, the National Institutes of Health (NIH) held a workshop on HSV vaccine research (31). There currently is no available, effective vaccine. The results of two randomized control trials of a recombinant glycoprotein vaccine recently were reported for prevention of genital HSV-2 infection (32). These trials evaluated a recombinant subunit vaccine containing 30 mg each of two major HSV-2 surface glycoproteins, called gB2 and gD2. Neutralizing antibodies are directed against this vaccine. The schedule for vaccination was administration of this dose at time 0 and 1 and 6 months later. A citrate buffer vehicle was given to the control subjects, and participants were

followed-up 1 year after the third immunization. All subjects were HSV-2 and human immunodeficiency virus (HIV) seronegative. In one of the trials, more than 500 HSV-2 seronegative partners of HSV-2–infected persons were vaccinated. In the other trial, more than 1,800 persons attending a sexually transmitted diseases clinic were evaluated. The major outcome was time to acquisition of HSV-2 infection as determined by either seroconversion or isolation of HSV-2 culture. Overall, acquisition of new HSV-2 infections was not significantly different between the groups (4.6 and 4.2 per 100 patient-years in the placebo and vaccine recipients, respectively) (p = NS). Although the vaccine induced high levels of HSV-2–specific neutralizing antibodies in vaccinated patients who either did or did not develop genital herpes, the vaccine had no significant effect on the duration of first clinical HSV-2 infection. Thus, this immunogenic vaccine had no effect on acquisition of new sexually transmitted HSV-2 infections. It has been suggested that this vaccine did not provide protection against acquisition of HSV-2 because it did not provide "sterilizing immunity" or effectively eradicate the invading pathogen after the initial infection (33). It is noted that HSVs are viruses that infect neuronal cells and establish latent infection. Thus, effective protection will require more than serum neutralizing antibodies. Possible avenues for future research include new vaccine strategies, perhaps use of live viral mutants, or DNA vaccines that can elicit both cellular and humoral immune responses. It will be necessary for vaccines to induce a more potent mucosal immune response to effectively interfere with the initial infection (33).

Supportive Treatment

Because most recurrent episodes last for only a few days and can be rather mild, some patients with recurrent disease can be managed without antiviral therapy. Measures such as frequent sitz baths, topical anesthetics, use of electric blow dryers (on cool setting), and treatment of secondary yeast infections are of benefit in decreasing symptomatology.

HERPES SIMPLEX VIRUS INFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Patients with immunocompromised disorders are subject to prolonged and/or severe episodes of genital or perianal herpes. Intermittent or suppressive therapy with oral antiviral agents often is beneficial. Although the dosage of antiviral drugs for HIV-infected patients with HSV is controversial, clinical experience strongly suggests that immunocompromised patients benefit from increased doses of antiviral drugs. Regimens such as acyclovir 400 mg orally three to five times a day have been useful. Therapy should be continued until clinical resolution is attained. An alternative regimen is famciclovir 500 mg twice a day. In doses recommended for treatment of genital herpes, valacyclovir, acyclovir, and famciclovir probably are safe for use in immunocompromised patients. For severe cases, acyclovir 5 mg/kg intravenously every 8 hours may be required. If lesions persist in a patient receiving acyclovir treatment, resistance of the HSV strain to acyclovir should be suspected. In these cases, alternative therapy should be administered. All acyclovir-resistant strains also are resistant to valacyclovir, and most are resistant to famciclovir. In such cases, foscarnet 40 mg/kg intravenously every 8 hours until clinical resolution is attained often is effective for treatment of acyclovir-resistant genital herpes cases (26).

GENITAL HERPES IN PREGNANCY AND NEONATAL HERPES INFECTION

Intense interest in this area has resulted in substantial progress in our understanding of pathophysiology. Previous treatment recommendations have been revamped and are described in the following.

Epidemiology

In surveys, the prevalence of asymptomatic shedding of herpes virus from the genital tract has been 0.1% to 4% of pregnant women. Of all gravidas with positive genital cultures for herpesvirus, the range of asymptomatic infection has been very broad (13% to 66%). Pregnancy, in general, does not appear to influence the recurrence rate of genital herpes or the severity of recurrent episodes. Primary episodes may be more severe during pregnant than nonpregnant women, but data are scant.

The neonate may acquire herpes infections either during pregnancy or during or immediately after birth. The former route (intrauterine infection) is rare; the latter (perinatal infection) is more common. Transplacental infection by herpesvirus has been recognized in the past as being rare and often devastating for the infant. Hutto and colleagues (11) summarized 13 culture-proved cases from nine institutions. Intrauterine (i.e., transplacental) infection was based on presentation within the first 7 days of life (as perinatally acquired infection has a later onset). During the course of the neonatal disease, skin lesions developed in 92% (but were not always present at or before diagnosis). Central nervous lesions were present in 92% and included microcephaly (54%), hydranencephaly (38%), and microphthalmia (15%). Overall, the results were devastating. Death occurred in 31%, and neurologic sequelae developed in nearly all survivors, even though antiviral chemotherapy was used in these neonates (11). Intrauterine infection appears to be a consequence solely of primary maternal infection.

Perinatal acquisition of HSV by the neonate usually is the result of contact with an infected maternal lower genital tract, but HSV (especially type 1) infection can be acquired from maternal or paternal oral-labial infection or from a hospital worker.

In the past 15 years, we have learned more about the risk of perinatal HSV infection. To understand current concepts, we must trace the developments over the last decade and a half. In the 1980s, primary infection, when diagnosed on the basis of severe clinical presentation or seroconversion, was associated with a 40% overall risk of major perinatal complications, including abortion, premature birth, growth restriction, and neonatal herpes. When primary infection occurred in the third trimester, the perinatal complication rate was 80% (4/5 cases) (10). At that time, nonprimary first episode infection, also diagnosed by clinical presentation or by serologic evidence of prior exposure to the heterologous HSV type, was not observed to be associated with serious sequelae (34). Recurrent episodes, diagnosed mainly by clinical criteria, were believed to be associated with neonatal acquisition but not with intrauterine infection. The risk of neonatal infection in an asymptomatic mother was estimated to be up to 4%, but the observed risk in an asymptomatically infected mother with a recurrent infection was 0% (95% confidence interval, 0%–8%) (35). Women with primary HSV genital infection were more likely to

shed virus asymptomatically. At visits later in the pregnancy, 10.6% of cultures were positive after primary first-episode infection versus 0.5% of cultures after nonprimary first-episode infection ($p < 0.01$).

An important question is: What is the risk of neonatal infection after delivery through a birth canal with an asymptomatic, recurrent HSV infection? Prober and colleagues (35) provided very pertinent data in 1987. They reported that after exposure to HSV at vaginal delivery, none of 34 infants developed infection (95% confidence interval, 0%–8%.) Antibody was present in all infants, and it was greater than 1:20 in 79% (35). Another important question is: What is the likelihood that a woman with a history of recurrent herpes will be shedding virus asymptomatically at the time of delivery? At other times in pregnancy, the reported rate is about 1% (30/2,485), with a range from 0.75% to 3%. On the day of delivery, Arvin et al. (36) noted a rate of asymptomatic shedding of 1.4% (5/354). The estimate of the risk of neonatal herpes from an *asymptomatic* mother with a history of *recurrent* genital HSV is less than 1 in 1,000.

In the early 1990s, concepts were revised because it was demonstrated that neonatal infection may develop after delivery from mothers with either symptomatic or asymptomatic infection and that transmission of virus to the neonate may occur whether the mother was having a primary, nonprimary, or recurrent infection. It became evident that the epidemiology of neonatal transmission is complex, even more so than previously thought. In 1991, Brown and coworkers (37) reported a large study to define the risk factors associated with neonatal acquisition of HSV. They performed genital cultures on nearly 16,000 women who were in early labor and were without symptoms or signs of genital HSV. Follow-up consisted of serologic testing and serial culturing for HSV. Herpes simplex virus was isolated from 0.35% (56/15,923) of these asymptomatic parturients. Of the 56 women, 51 had HSV-2 and five had HSV-1. In 18 (35%) of these 56 women, there was serologic evidence of recently acquired subclinical first-episode HSV infection, and in 34 women (65%) there was evidence of reactivation infection. Neonatal HSV infection developed in 33% (6/18) of infants born to mothers with a first-episode infection and in only 3% (1/34) of infants born to women with reactivation of HSV ($p < 0.01$). Neonatal HSV also developed in three of the infants born to 15,867 women with negative cultures, presumably because of either false-negative cultures or nosocomial or neonatal acquisition. Several factors appeared to influence transmission of HSV from mother to neonate: HSV type, the mother's clinical stage of infection, anatomic site of viral shedding, use of fetal scalp electrodes, and the specificity of passively transferred HSV antibodies from mother to infant. The rate of neonatal transmission was ten times higher when infants were born to mothers with recently acquired first episodes than when infants were born to mothers with reactivation. Among women with first-episode infection, the rate of neonatal infection was similar, whether the infection was primary (2/5 [40%]) or nonprimary (4/13 [31%]). The passive transfer of maternal antibodies to HSV-2 (but not HSV-1) appeared to be protective. Further, viral shedding from the cervix was associated with an increased risk of transmission. Neonatal transmission occurred in two of ten neonates when there was shedding from the cervix only and in one of 34 infants when there was shedding only from the labia ($p < 0.01$). Fetal scalp electrodes were used in all seven cases in which neonatal HSV developed and in 23 of 49 infants (47%) exposed to HSV during delivery but without neonatal HSV ($p < 0.01$).

Other recent data also suggest some protective value from previous immunity to

HSV-1. Boucher et al. (38) used type-specific antibodies to glycoprotein G in serial blood samples of 1,891 pregnant women. Of these women, 311 (16.5%) had past immunity to HSV-2. Four of 1,580 women seroconverted to HSV-2 during pregnancy, at an annualized rate of 0.58%. Three of these four infections were asymptomatic, and all had preexisting HSV-1 immunity. None of the women and none of the neonates experienced any adverse consequences. Based on these small numbers, Boucher and coworkers believed that asymptomatic primary episodes in women with previous HSV-1 immunity may be of less consequence neonatally than true primary HSV-2 infection.

From a CDC surveillance for neonatal HSV infections, Stone and colleagues (39) reported an 18-month study of 184 cases. Only 22% of mothers had a history of HSV infection, and in only 9% were there genital lesions identified at the time of delivery. Demonstrating that cesarean delivery may not be protective, there were 15 cases of neonatal HSV even though cesarean delivery had been performed prior to membrane rupture (39).

In the late 1990s, concepts about perinatal transmission of HSV were revised again, based on two important publications (4). In 1997, Hensleigh et al. (4) reported the distribution of HSV infections in severe first episodes in pregnancy. They classified HSV infection on the basis of culture, type 2 specific antibodies, and nontype-specific antibody. Even though the clinical picture was so severe that it was suggestive of primary infection to these expert clinicians, most cases were, in fact, recurrences (Fig. 6.2). Outcome results were available in 20 of the pregnancies with “severe” genital HSV infections. Premature birth occurred in just one (5%), and intrauterine growth retardation and neonatal HSV infection occurred in none. Thus, the important contributions from this recent work are as follows. (i) Correct classification of HSV infection in pregnancy requires clinical correlation with viral isolation and type-specific serology, even when the clinical presentation is severe and suggestive of primary infection. (ii) “Severe” first episodes usually are not primary and as such are not commonly associated with adverse perinatal complications.

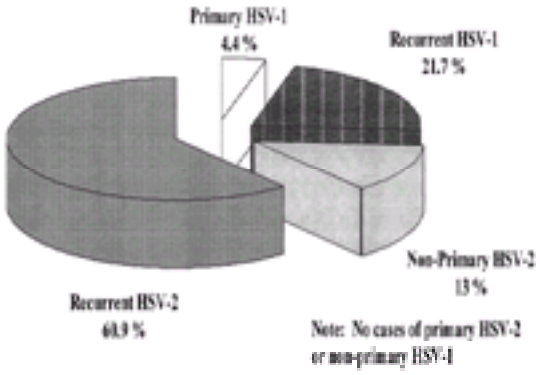


FIGURE 6.2. Distribution of herpes simplex virus infection in severe first episodes in pregnancy (n = 23). Clinical picture suggestive of primary infection. (From Hensleigh PA, Andrews WW, Brown Z, et al. Genital herpes during pregnancy: inability to distinguish primary and recurrent infections clinically. *Obstet Gynecol* 1997:89:891–895, with permission.)

In another large study from the University of Washington, serum samples were collected at the first prenatal visit, at 14 to 18 weeks, at 24 to 28 weeks, and delivery (10). Type-specific antibodies were determined by Western blot to HSV-1 and HSV-2, and genital cultures for HSV were performed on admission. Overall, 1.3% of subjects (94/8,538) seroconverted during pregnancy. Of these, 32% seroconverted to HSV-1 and 68% seroconverted to HSV-2. Of note, 36% of the seroconversions were symptomatic, whereas 64% were subclinical. The HSV antibody status of patients at the first visit was as follows: 48% were positive to HSV-1 alone, 11% were positive to HSV-2 alone, 17% were seropositive to HSV-1 and HSV-2, and 24% were negative to both HSV types. Comparing neonates of 94 mothers with seroconversion to those of 6,009 without seroconversion, Brown and colleagues observed no differences in mean birthweight, gestational age, or rates of intrauterine growth retardation, stillbirth, or neonatal death (10). They observed no infected newborns among the 94 mothers who seroconverted during pregnancy (95% CI, 0%–3.2%). A small subgroup of nine patients provides considerable insight into the pathophysiology. There were nine women who demonstrated recent acquisition of genital HSV based on having positive culture in labor but not having existing homologous antibody. As shown in Fig. 6.3, these nine mothers developed 4 (44%) infants with neonatal infection. The characteristics of HSV infections in pregnancy are summarized in Table 6.5. Our current understanding of genital HSV is summarized in Box 3.

Box 3

Current Understanding of Genital Herpes Simplex Virus Infection

- HSV infection is common in all groups in United States and has increased by 30% since the late 1970s (37).
- Most HSV infections are acquired “asymptomatically”; seropositive patients usually do not report a positive history (37).
- Polymerase chain reaction is a far more sensitive diagnostic technique than culture (19).
- Classification of first episodes of genital HSV infection *cannot* be made correctly by clinical criteria alone (4).
- Risk of neonatal infection seems to be very low when there has been development of homologous (type-specific) maternal antibody.
- These antibodies are protective for neonate (4,10).
- Newborns at highest risk are those born to women who shed virus (even asymptomatically) and who have not developed antibody (10,37).

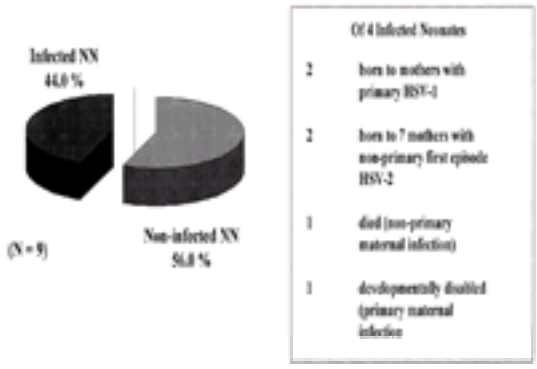


FIGURE 6.3. Recent acquisition of genital herpes simplex virus and neonatal infection. Mothers had positive culture in labor, but did not have homologous antibody. (From Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during Pregnancy. *N Engl J Med* 1997;337:509–515, with permission.)

Characteristics	Primary Infection	Recurrent Infection	Nonprimary First Episode Infection
Maternal symptoms	Asymptomatic to severe	Same	Same
Fetal-neonatal infection risks	Transplacental and neonatal	Neonatal	Mainly neonatal
Estimated neonatal risk	Up to 40% or higher[a]	<1% to 4%	Up to 40%

[a]Depending upon presence or absence of maternal antibody.

TABLE 6.5. REVISED SUMMARY OF HERPES SIMPLEX VIRUS INFECTIONS IN PREGNANCY

The course of neonatal HSV infection has been described more fully in recent publications. Neonatal infection may take one of three forms: disseminated; central nervous system (CNS); or skin, eye, or mouth only. Disseminated disease has high mortality and morbidity, even when current antiviral agents (acyclovir or vidarabine) are used (Table 6.6) (40,41 and 42). Neonatal infection of the CNS has a lower mortality but still a high morbidity. Skin, eye, or mouth only infection has both low mortality and low morbidity when antiviral agents are used. The NIH Collaborative Antiviral Study Group compared presentation of neonatal HSV from 1973 to 1981 with 1982 to 1987 (41). In the latter period, the frequency of disseminated disease decreased from 51% to 23%, whereas the frequency of skin, eye, or mouth only disease increased from 18% to 44%. The proportion of cases presenting as CNS infection remained about the same (32 vs. 34%). The authors noted that the most likely explanation was recognizing and treating skin, eye, or mouth only infection

before it progressed to disseminated disease.

	Deaths		Normal at 1 Year	
Type of Infection	Vidarabine	Acyclovir	Vidarabine	Acyclovir
Skin, eye, or mouth only	0	0	88% (22/25)	98% (45/46)
Central nervous system	5 (14%)	5 (14%)	43% (13/30)	29% (8/28)
Disseminated	14 (50%)	11 (61%)	58% (7/12)	60% (3/5)

From Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991;324:444–449.

TABLE 6.6. CONTROLLED TRIAL OF VIDARABINE VS. ACYCLOVIR IN NEONATAL HERPES SIMPLEX INFECTION

PREVENTION OF NEONATAL HERPES INFECTION

Despite more than 30 years of research, there is still no foolproof approach to prevent most cases of neonatal HSV infection (42,43). In the original studies of Amstey and Monif (8) and Nahmias and colleagues (9), the risk of neonatal herpes increased markedly when cesarean section was performed after the membranes had been ruptured for 4 or more hours. Accordingly, it had been widely held that with membrane rupture of this duration or longer, there was no advantage in preventing neonatal herpes by performing a cesarean section (44). Yet, many of the cesarean sections carried out after 4 hours of membrane rupture may have been performed after many vaginal examinations, many hours of labor, and much longer intervals of membrane rupture. Current recommendations have reconsidered the value of cesarean section to prevent neonatal herpes, even when the interval of membrane rupture has been over 4 hours.

Until 1988, weekly viral cultures to detect asymptomatic HSV shedding in late pregnancy was the recommended policy. In the presence of a positive culture, cesarean delivery was recommended. In studies, the cesarean delivery rate for prevention of herpes was 20% to 40%, and there were no infected infants. Subsequently, a case of serious neonatal HSV-2 infection was documented (in the second twin) of a woman who had been followed carefully with weekly cultures (45). Although the infant survived, it had psychomotor retardation, seizures, and other neurologic sequelae. This failure of the weekly cultures to prevent neonatal infection was documented by showing that the isolates from mother and infant had a similar DNA structure and were likely the same virus. In addition, in a CDC surveillance study of neonatal HSV, there were 15 cases that developed despite the performance of cesarean delivery prior to membrane rupture (39).

Further criticism of the weekly cultures came from a decision analysis in which it was estimated that the weekly viral culture diagnosed only 25% of subclinical recurrent

infections at delivery. This estimation was based on knowledge that the average episode of asymptomatic shedding lasts only 3 to 5 days. Further, it was estimated that with weekly viral cultures, the cost per case of neonatal herpes invested is $1,800,000 (46). In a later decision analysis, it was estimated that weekly screening cultures would prevent only 1.8 cases of neonatal HSV annually in the United States, at a cost of more than $37 million dollars per case averted (47). The most convincing data against weekly viral cultures came from a 1987 study showing the failure of antepartum cultures to predict culture status at delivery. Of 414 pregnant women with recurrent HSV infection, 17 had positive antepartum cultures. None of these was positive at delivery. Of 354 asymptomatic mothers, 5 (1.4%) were positive at delivery, but none had positive antepartum cultures (36).

In November 1988, an American College of Obstetricians and Gynecologists (ACOG) Technical Bulletin summarized recommendations as follows (48):

- Cultures should be done when a woman has active HSV lesions during pregnancy to confirm the diagnosis. If there are no visible lesions at the onset of labor, vaginal delivery is acceptable.
- Weekly surveillance cultures of pregnant women with a history of HSV infection, but no visible lesions, are not necessary and vaginal delivery is acceptable.
- Amniocentesis in an attempt to rule out intrauterine infection is not recommended for mothers with HSV infection at any stage of gestation.

The ACOG further recommended that “term patients who have visible lesions and are in labor or who have ruptured membranes should undergo cesarean delivery ... even with membranes ruptured for more than 24 hours.”

A few months earlier, the Infectious Disease Society for Obstetrics and Gynecology made similar recommendations, including the emphasis that the history of genital herpes in the pregnant woman or in her partner(s) should be solicited and recorded in the prenatal record (49). Further, in women with herpetic lesions of the genital tract when either labor or membrane rupture occurs, cesarean delivery is a technique that can reduce the risk of neonatal herpes virus infection. Ideally, cesarean section should be performed before or within 4 to 6 hours of membrane rupture, but cesarean delivery may be of benefit in preventing neonatal herpes regardless of duration of membrane rupture.

A decision analysis also concluded that physical examination in labor is the optimal strategy if the primary goal is to minimize the ratio of excess cesarean deliveries to cases of neonatal HSV infection averted (50). Another decision analysis supported the positions regarding the recommendations to abandon weekly cultures (47).

In 1993, Randolph and coworkers (51) provided a provocative and thorough decision analysis, which argued that the current practice of cesarean delivery for women with a history of genital herpes that recurs at delivery results in maternal morbidity and mortality and costs that exceed the neonatal benefits. Using data from a MEDLINE search and opinion from experts, they estimated that the current approach for women with recurrences, as recommended by ACOG, results in more than 1,580 excess cesarean deliveries performed for every poor neonatal outcome prevented and a cost per neonatal herpes case averted of $2.5 million. On the other hand, these authors estimated that cesarean delivery for women with first-episode lesions

at the time of delivery has low maternal costs per neonatal benefit and does save money. In an accompanying editorial, we believed that changing clinical practice solely on the basis of this decision analysis would be premature because the quality of the data is poor and the sequelae are potentially great (49,52). For the present, we advise clinicians caring for a woman with either recurrent or first-episode genital herpes lesions at the time of delivery to continue to perform cesarean delivery as long as there are no contraindications. Management of the neonate with inadvertent exposure to an HSV-infected maternal genital tract has been described (53). Parents and primary care providers should be informed regarding symptoms and signs of infection. If the maternal infection is a recurrence, some clinicians obtain neonatal cultures for 4 to 6 weeks as an option, but this is not a standard, and there are no data to support this. If the maternal infection was a first episode, the recommendation is that viral cultures be performed from the neonate (urine, stool, eyes, throat, and cerebrospinal fluid [CSF]). If any of these cultures is positive for a neonate who is older than 48 hours or if the CSF findings are abnormal, then the recommendation is to initiate intravenous acyclovir therapy (53). A more recent recommendation from the American Academy of Pediatricians and ACOG for infants born vaginally to mothers with active primary genital herpes is to obtain cultures for HSV from the eye, mouth, and rectum and to begin empiric treatment with acyclovir 10 mg/kg intravenously every 8 hours for 7 to 10 days. It also is recommended to observe the infant closely for signs and symptoms of disease. The Guidelines for Perinatal Care acknowledges that management of infants born vaginally to women with active recurrent genital herpes lesions is less clear (54). Most experts recommend HSV culture at 24 to 48 hours of life and acyclovir therapy in this circumstance, only if clinical signs develop and/or cultures are positive. Some experts, it is acknowledged, recommend empiric acyclovir therapy, especially if the recurrent disease is extensive. Infants born by cesarean delivery to a woman with active genital lesions with intact membrane should be observed carefully and cultured for HSV even though the risk of transmission is low. Special isolation precautions are not needed for most of these neonates. They should be observed in the nursery and followed closely after discharge. Parents should be instructed to report early signs of infection.

Genital Herpes Infection With Preterm Premature Rupture Of The Membranes

This rare combination of problems presents a difficult decision between delivery of a premature infant and expectancy with the potential for serious neonatal herpes infection. For pregnancies with a high neonatal survival rate, cesarean delivery would be appropriate. However, for pregnancies of less than 31 to 32 weeks, the choice is less clear. Three case reports provide some guidance (52,55). In all cases, the pregnancies were between 25 and 30 weeks' gestation, and herpes was diagnosed clinically as well as by culture or Papanicolaou smear. Expectancy was followed in all (with use of intravenous acyclovir in one). In these three cases, delivery occurred 1 to 5 weeks later, with all infants negative for HSV. Although the reported experience is small, it suggests that expectancy is appropriate in cases of marked prematurity.

Delivery In Pregnancies With “Remote” Herpes Simplex Virus Lesions

In women who have herpes lesions remote from the vulva (i.e., on buttocks, thighs, back, and lower abdomen), the question arises as to whether a vaginal route for delivery is appropriate. Pertinent information has been provided to determine asymptomatic cervical infection in women with clinical episodes of HSV in these

anatomic locations. Over 90% of HSV isolates in the lesions were type 2. Observations suggest that the risk of concomitant asymptomatic cervical infection is low and probably not very different from the 1% to 2% rate of asymptomatic infection in patients with recurrent genital herpes. Thus, for a woman with recurrent lesions remote from the vulva, vaginal delivery would seem appropriate, provided the lesions can be covered with surgical drapes and thus placed out of the field of vaginal delivery, and provided careful inspection of the vulva, vagina, and cervix reveals no lesions.

Use Of Fetal Scalp Electrodes

A few cases have been reported in which neonatal HSV infection may have been introduced or worsened because of use of a scalp electrode. In most cases (four of six), the mothers had subclinical infection. Brown and colleagues (37) found that scalp electrode use was associated with neonatal infection (as described earlier). The ACOG maintains that “monitoring by fetal scalp electrode is not contraindicated if needed to adequately assess fetal condition in women with a history of HSV but without symptoms or lesions” (48).

USE OF ACYCLOVIR IN LATE PREGNANCY FOR PREVENTION OF NEONATAL INFECTION

There is widespread agreement that acyclovir should be used when there is disseminated or life-threatening maternal infection, as it has been used in such cases in late pregnancy without apparent adverse effects (48). Two reports have detailed registry cases of acyclovir use in pregnancy. In 1992, Andrews and colleagues (56) noted 312 acyclovir-exposed pregnancies, including 239 in the first trimester. There was no increase in the number of birth defects and no consistent pattern of abnormalities. There was no increase in spontaneous abortion compared with expected rates. These data were expanded in late 1993 (57), and the results are shown in Table 6.7. There were 601 exposed pregnancies, with 425 in the first trimester. Although the registry findings showed no increase in risk for birth defects among infants born to acyclovir-exposed women, CDC officials point out that the current sample size is sufficient to detect a risk twofold greater than the baseline rate of 3%, but it is not sufficient to detect smaller risks if such exist.

	Earliest Trimester of Exposure			
Outcome	First	Second	Third	Total
Birth defects	13	1	2	16
No birth defects				
Live births	298	68	104	470
Spontaneous fetal losses	47	0	1	48
Legal induced abortions	67	0	0	67
Total	425	69	107	601

Adapted from Centers for Disease Control. Pregnancy outcomes following systemic prenatal acyclovir exposure—June 1, 1984–June 30, 1993. MMWR 1993;42(RR-41):806–809.

TABLE 6.7. ACYCLOVIR USE DURING PREGNANCY AND OUTCOME JUNE 1,

1984–JUNE 30, 1993

Limited data exist to determine whether use of acyclovir in the last few weeks of pregnancies complicated by HSV infection is of benefit. In a letter, Stray-Petersen (58) reported that such use of acyclovir compared with no treatment (46 women in each group) led to fewer positive HSV cultures (0% vs. 17%; $p < 0.001$) and fewer cesarean deliveries for HSV infection (0% vs. 20%; $p < 0.001$). There were no cases of neonatal HSV infection in either group (58). In another preliminary report, Scott and coworkers (59) conducted a randomized blinded study among women with first episode HSV infection. No serologic studies were performed to determine whether these first episodes were true primary infection or nonprimary first episodes. At 36 weeks' gestation, patients were randomized to receive either acyclovir 400 mg twice a day or placebo on the same schedule. The outcome measures were cesarean section for clinical recurrence and neonatal HSV culture positivity. The results of the trial are shown in Fig. 6.4. Overall, mothers who received acyclovir had significantly fewer infections at the time of delivery and significantly fewer cesarean sections for HSV infection. However, there was not a significant reduction in overall cesarean section rate because of more cesarean sections in the placebo group for other indications. There were no neonatal infections, and no adverse effects of acyclovir were detected. In a study of five pregnant women, Haddad and colleagues (60) found that acyclovir after 37 weeks failed to suppress asymptomatic shedding in one woman, even though levels were adequate and comparable to those in nonpregnant adults. A recent clinical decision analysis laid out the considerations regarding use of acyclovir in late pregnancy and noted the absence of any clinical trials. This decision analysis considered the most effective strategy was acyclovir with cesarean section if breakthrough recurrences happened at the time of labor. This strategy prevented 5.5 cases of neonatal herpes for every 10,000 women treated with acyclovir, with 216 of these women undergoing delivery by cesarean section (61).

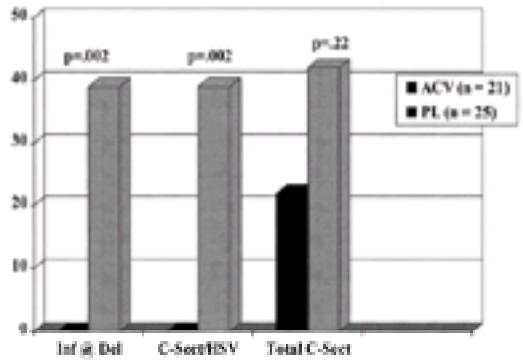


FIGURE 6.4. Results of acyclovir suppression in late pregnancy. No neonatal infection or adverse effects are seen. (From Scott L, Jackson G, Sanchez P, et al. Prevention of cesarean section for recurrent genital herpes simplex virus (HSV) using acyclovir suppressive therapy. *Obstet Gynecol* 1996;67:69–73, with permission.) ACV, acyclovir; PL, placebo.

In a kinetic study of acyclovir in late pregnancy, Frenkel and coworkers (62) studied doses of 200 and 400 mg every 8 hours from 38 weeks until delivery. Levels achieved a steady-state concentration of 1.9 ± 1.0 mol/L and 3.3 ± 1.0 µmol/L for the lower and higher doses, respectively. Acyclovir did not concentrate in the fetus. The kinetics were similar to those of nonpregnant adults. Acyclovir was well tolerated and did not appear to have any toxicity.

Data regarding the kinetics of acyclovir in pregnancy are favorable, but data regarding efficacy for suppression in late pregnancy are limited. Safety data appear encouraging, but accumulated experience still is insufficient to rule out potential small risks. Currently, the CDC recommendations are not to use acyclovir for suppression near term (26).

MANAGEMENT OF THE INFECTED MOTHER DURING HOSPITALIZATION

Whether the delivery has been by the vaginal or abdominal route, the infected women should be educated regarding thorough hand washing and good hygiene to prevent neonatal infection. As noted by ACOG, “every effort should be made to avoid direct contact of the newborn with herpetic lesions” (48). The clinically infected mother may handle her infant, provided she observes thorough hand washing and is wearing a clean cover gown. It is unlikely that breast-feeding by a woman with active genital herpes poses any clear risk to the newborn.

Isolation and special infection control precautions are not necessary for a woman with a history of genital herpes but without lesions at the time of delivery or the immediate puerperium (49).

Because herpes infection may result in serious untoward effects in newborns, it is essential to fully educate the mother regarding the reasoning behind these precautions. The summary recommendations for management of genital HSV in pregnancy for recurrent infection, first-episode infection, and in labor are given in Box 4, Box 5, and Box 6, respectively.

Box 4

Management of Genital Herpes Simplex Virus in Pregnancy: Recurrent Infection

- Counsel, education, reassure
- Do not perform routine cultures
- Examine on admission to labor and delivery unit
- Anticipate vaginal delivery
- Acyclovir prophylaxis is not established

Box 5

Management of Genital Herpes Simplex Virus in Pregnancy: First-Episode Infection

- Consultation may be appropriate
- Establish HSV infection as primary, nonprimary, or recurrent, if possible
- Educate and evaluate for intrauterine growth retardation, intrauterine fetal death, preterm labor, and neonatal infection, when appropriate
- Acyclovir prophylaxis to prevent maternal recurrences is not established

Box 6

Management of Genital Herpes Simplex Virus in Pregnancy: In Labor

- If there is a lesion or a typical prodrome, perform a cesarean delivery, ideally before membrane rupture
- If there is no infection, allow vaginal delivery
- Inform nursery about maternal history

HERPETIC WHITLOW

Herpetic whitlow is a cutaneous HSV infection, most commonly of the finger or thumb and often occurring at the site of previous minor trauma. Whitlow is an occupational hazard for medical/dental personnel.

Typically, the onset of symptoms is sudden, occurring 3 to 7 days after exposure. The contact with an infected patient is recognized. Most often, one digit is involved, but multiple digits are infected in about 10% of cases. Initial local symptoms are edema, erythema, pain, and tenderness. Promptly, one or more vesicles appear. Local symptoms increase, and fever, chills, lymphangitis, and lymphadenopathy develop. Vesicles often coalesce and ulcerate, and the fluid commonly becomes opaque. At this point, the underlying problem may be misdiagnosed as a paronychia or other bacterial infection. This is unfortunate, because surgical intervention is clearly contraindicated for whitlow, as it increases morbidity. Thus, there must be a high index of suspicion, especially in health care workers. After 10 to 14 days, symptoms subside and lesions begin to heal.

Treatment consists of analgesics, elevation, and immobilization. Antibiotics are of value only when there is a secondary bacterial infection. We emphasize that surgical intervention is contraindicated.

Recurrences are common, especially in the first month, with subsequent recurrences being highly variable. One report noted use of intravenous acyclovir in a dentist with a first-episode whitlow. Because of dramatic response (96 hours after therapy was

started), the authors believed acyclovir was of benefit. The dentist had no recurrences in 12 months (63).

Anecdotal experience in a surgical resident has suggested that oral acyclovir (e.g., 200 mg three times a day) may suppress frequent severe episodes. Gill et al. reported use of oral acyclovir as early therapy at the first warnings of recurrence in eight patients who had at least six previous recurrences of whitlow. Treatment was 800 mg orally twice daily for 5 days. Acyclovir initiated during the prodrome appeared to be effective in all, as the initial symptoms resolved promptly and no lesions appeared (64).

To prevent whitlow, use of gloves is recommended when there is direct contact with oral, pharyngeal, or genital secretions, even if there are no signs of active HSV infection. For the employee with a herpetic whitlow, use of a glove on the involved hand is recommended while working in a patient care area. It would seem wise to exclude these workers from maternity or neonatal units, although clear data on transmissibility are not available. Use of acyclovir may be considered.

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7

SEXUALLY TRANSMITTED DISEASES

As we enter the new millennium, the virtual revolution in the field of sexually transmitted diseases (STDs) continues. Although in many industrialized countries, the role of STDs is decreasing, the United States remains in the midst of an epidemic of STDs (1). From the classic five venereal diseases—gonorrhea, syphilis, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale—the number of STD agents has expanded to include more than 30 microorganisms (2) (Table 7.1). This expansion partly resulted from the recognition that many known pathogens were sexually transmitted (e.g., cytomegalovirus [CMV], hepatitis B virus [HBV], hepatitis C virus [HCV}, intestinal bacteria, and parasitic organisms) (2). Since 1975 there have been 12 new sexually transmitted pathogens identified (Table 7.2) (2). These include organisms that appeared as new infections (e.g., human immunodeficiency virus types 1 and 2 [HIV-1 and HIV-2]) and organisms discovered as the result of new diagnostic tests (e.g., *Mycoplasma genitalium* and *Helicobacter fennelliae*). Sexual transmission is not definitely established for a few of these organisms but is very likely based on available clinical epidemiologic evidence (2). Additionally, the spectrum of sexually transmitted infections has expanded to include diseases such as nongonococcal urethritis, epididymitis, vaginitis, cervicitis, pelvic inflammatory disease (PID), infertility, perinatal infections, hepatitis, enteric infections, arthritis syndromes, genital oncogenesis, and severe immunosuppression such as acquired immunodeficiency syndrome (AIDS) (Table 7.3). Syndromes and complications of STDs specific to women are listed in Table 7.4.

Bacterial agents	Viral agents
Neisseria gonorrhoeae	Human Papillomavirus (>25 genital types)
Chlamydia trachomatis	Herpes simplex virus
Treponema pallidum	Hepatitis A virus
Gardnerella vaginalis	Hepatitis B virus
Haemophilus ducreyi	Hepatitis C virus
Shigella	Cytomegalovirus
Campylobacter	Molluscum contagiosum virus
Group B streptococcus	Human immunodeficiency virus type 1, type 2, subtype O
Mobiluncus curtisii, Mobiluncus mulieris	Human T-cell lymphoma/leukemia virus types I and II
Helicobacter fennelliae, Helicobacter cinaedi	Human herpesvirus type 8
Genital mycoplasmata	Protozoan agents
Mycoplasma hominis	*Trichomonas vaginalis*
Ureaplasma urealyticum	*Entamoeba histolytica*
Mycoplasma genitalium	*Giardia lamblia*
Fungal agents	Ectoparasites
Candida albicans	*Phthirus pubis*
	Sarcoptes scabiei

TABLE 7.1. SEXUALLY TRANSMITTED PATHOGENS

Pathogen	Year identified
Human papillomavirus (>25 genital types)	1976–present
HTLV types I and II	1980–1982
Mycoplasma genitalium	1981
Mobiluncus curtisii, Mobiluncus mulieris	1981
Helicobacter fennelliae, Helicobacter cinaedi	1985
HIV type 1, type 2, subtype O	1983, 1986, 1990
Hepatitis C virus	1989
Human herpesvirus type 8	1995

HTLV, Human T-cell lymphoma/leukemia virus; HIV, human immunodeficiency virus.
Source: From Eng TR, Butler WR, eds. *The hidden epidemic: confronting sexually transmitted diseases*. Washington: Institute of Medicine National Academy Press, 1997, with permission.

TABLE 7.2. SEXUALLY TRANSMITTED PATHOGENS NEWLY IDENTIFIED OR NEWLY EMERGENT SINCE 1975

TABLE 7.3. SEXUALLY TRANSMISSIBLE PATHOGENS AND ASSOCIATED DISEASE SYNDROMES

TABLE 7.4. SYNDROME AND COMPLICATIONS OF SEXUALLY TRANSMITTED PATHOGENS IN WOMEN

STDs are significant social, health, and economic burdens worldwide (1). It has been estimated that STDs (excluding HIV) are the second leading cause of lost healthy life among women aged 15 to 44 years in the developing countries of the world (3,4). As noted by the Institute of Medicine (IOM) (1), the World Health Organization (WHO) estimated that in 1995, there were 333 million new cases worldwide of the four curable STDs: gonorrhea, 62.6 million; syphilis, 12.2 million; chlamydia, 89.1 million; and trichomoniasis, 167.2 million, among persons aged 15 to 49 years (5).

The IOM estimated that approximately 12 million new cases of STDs occur annually in the United States as of 1993 (1). These numbers result in the United States having the highest rates of curable STDs in the developed world (1). Of the top ten most frequently reported diseases in the United States in 1995, five were STDs (Table 7.5). STDs accounted for 87% of the top ten most frequently reported diseases in the United States (7). The economic impact of this "hidden epidemic" of STDs is substantial. The IOM committee estimated that the total costs for a selected group of major STDs and related syndromes (excluding HIV) were approximately $10 billion in 1994 (1). This underestimates the full cost because it did not include common STDs and associated syndromes such as bacterial vaginosis and trichomoniasis. The estimated annual cost of sexually transmitted HIV infection was nearly $7 billion, which brings the total cost of STDs in the United States to nearly $17 billion in 1994 (1). More recently in 1998, the American Social Health Association estimated that 15 million new STD cases occur annually in the United States (Table 7.6) (8).

1.	Chylamydia[a]
2.	Gonorrhea[a]
3.	Acquired immunodeficiency syndrome[a]
4.	Salmone iliosis
5.	Hepatitis A
6.	Shigellosis
7.	Tuberculosis
8.	Syphilis (primary and secondary)[a]
9.	Lyme disease
10.	Hepatitis B[a]

[a]Sexually transmitted disease.
Source: From CDC MMWR 1996;45:883–884.

TABLE 7.5. MOST COMMONLY REPORTED NOTIFIABLE DISEASES IN THE UNITED STATES 1995

Sexually Transmitted Disease	Incidence	Prevalence
Chlamydia	3 million	2 million
Gonorrhea	650,000	—
Syphilis	70,000	—
Genital herpes simplex virus type 2	1 million	45 million
Human papillomavirus	5.5 million	20 million
Hepatitis B	120,000	750,000
Trichomoniasis	5 million	—
Bacterial vaginosis	—	—
Human immunodeficiency virus	20,000	560,000
Total	15.4 million	

Source: From Cates W, and the American Social Health Panel. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. *Sex Transm Dis* 1999;26(Suppl):S2–S7, with permission.

TABLE 7.6. ESTIMATED INCIDENCE AND PREVALENCE OF SEXUALLY TRANSMITTED DISEASES IN THE UNITED STATES, 1996

Sexually active adolescents have the highest rates of STDs of any age-groups (9). The Centers for Disease Control and Prevention (CDC) estimates that every year, approximately 3 million adolescents in the United States acquire an STD (10). Several factors have been suggested as the explanation of why adolescents and young adults are at greater risk for acquiring an STD. These include the following: (a) They are more likely to have multiple partners; (b) they may be more likely to engage in unprotected intercourse; (c) their partners may be at higher risk of being infected; and (d) they are more susceptible to cervical infections with gonorrhea and chlamydia (11,12,13 and 14).

Cates (15) described the changing emphasis in the field of STDs. He noted an evolution from concern for the traditional venereal diseases, such as gonorrhea and syphilis, to emphasis on the syndromes associated with *Chlamydia trachomatis,* herpes simplex virus (HSV), and human papillomavirus (HPV), and recently to concern with the fatal disease AIDS, caused by HIV. With the exception of HIV, this redirection does not reflect the emergence of new pathogens but is the result of several factors: (a) The improvement in laboratory diagnostic techniques facilitates epidemiologic investigations that help elucidate the extent, transmission of, and the consequences of STDs; (b) increasing numbers of sexually active young adults are at risk for STDs; (c) age-adjusted incidences for the newer STDs, such as *C. trachomatis,* HSV, and HPV, have increased dramatically; and (c) whereas the traditional STDs, gonorrhea and syphilis, were easily cured with antimicrobial therapy, the newer STDs are associated with incurable and fatal conditions—HIV and AIDS, HPV associated with genital cancers, and chronic recurrent HSV. Additionally, the major impact of STDs on maternal and child health has been recognized. An increasing proportion of infections that are spread by multiple modes are being transmitted sexually; these include HBV, CMV, and various enteric pathogens.

It is also notable that with the exception of AIDS, STDs are associated with more serious long-term consequences in women than in men. These complications include (a) an increased risk for genital cancer with HPV; (b) loss of reproductive capability and ectopic pregnancy secondary to damage to the fallopian tubes with *Neisseria gonorrhoeae* and *C. trachomatis*; (c) complications of pregnancy, including spontaneous abortion, stillbirth, chorioamnionitis, preterm birth and low birthweight; and (d) transmission of serious or fatal infections to the fetus or newborn, such as syphilis, HSV, *C. trachomatis,* CMV, or HBV.

Recently, Bolan et al. (16) reviewed gender perspectives and STDs. They noted that in women, susceptibility to STDs and their sequelae is a function of several physiologic factors including (a) type of epithelial lining of the lower genital tract; (b) resident flora and pH levels of the vagina; (c) characteristics of cervical mucus; (d) patency of the endocervical canal; (e) phase of the menstrual cycle; and (f) immunologic capabilities of the individual. For instance, with the onset of puberty, estrogen stimulates development of squamous epithelium in the vagina and columnar epithelium becomes limited to the cervix. Because *C. trachomatis* and *N. gonorrhoeae* attach to columnar epithelium, the cervix becomes the primary site for infection with those organisms, particularly in early adolescence when the squamocolumnar junction tends to be on the ectocervix (16). Similarly, with the onset of puberty, the vaginal flora shifts to one predominated by lactobacilli (particularly hydrogen peroxide producers) and the pH level decreases to the 4.0 to 4.5 range

(17). These changes have been postulated to inhibit the growth of some STD organisms, including HIV (17,18).

In the reproductive age years, the major physiologic changes influencing the risk of STDs are related to the menstrual cycle, pregnancy, and contraceptive use (16). The menstrual cycle influences the risk for acquiring infection of the upper genital tract, and chlamydial and gonococcal acute PID most commonly occur at the end of or just after the menses (19). Pregnancy is associated with physiologic and immunologic changes that can affect the risk of STDs and their sequelae (20). As an example, the immune suppression seen in pregnancy can lead to accelerated progression or expression of HPV and increased frequency and severity of genital herpes recurrences (16).

Gender differences are also seen in the transmission of STDs (16). It appears that STD pathogens that cause discharge or are found in genital secretions (e.g., *N. gonorrhoeae, C. trachomatis,* HIV, and HBV) generally are transmitted more efficiently from men to women (21,22,23,24 and 25). In contrast, those STD organisms that result in genital ulcers or lesions (e.g., HSV, *Treponema pallidum,* or *Haemophilus ducreyi*) seem to be transmitted from men to women as efficiently as from women to men (26).

An epidemiologic synergy exists among STDs (27). They are historically, biologically, behaviorally, economically, and programmatically related. The ulcerative STDs (syphilis, chancroid, HSV) are associated with increased risk of acquiring and transmitting HIV (3). STDs that cause cervical discharge (e.g., gonorrhea, chlamydia, and trichomoniasis) are also implicated in enhancing transmission of HIV. The immunosuppression associated with HIV infection worsens other STDs and makes them more difficult to treat.

GONORRHEA

Gonorrhea, which is caused by the Gram-negative diplococcus, *N. gonorrhoeae,* remains a common reported communicable disease in the United States, with more than 350,000 cases reported in 1998 (second only to chlamydia) (1). Because of underreporting, it is estimated that approximately 700,000 cases of *N. gonorrhoeae* infection actually occurred in 1998 in the United States. Unfortunately the reported cases of gonorrhea in 1998 represented an 8.9% increase from 1997, the first increase since 1985. Although the reported annual incidence of gonorrhea in the United States has decreased dramatically from the peak of 1 million cases reported in 1975 (Fig. 7.1), the disease still remains common in the United States, as it does in most of the developing countries (2). On the other hand, gonorrhea has become rare in Canada and much of western Europe (2).

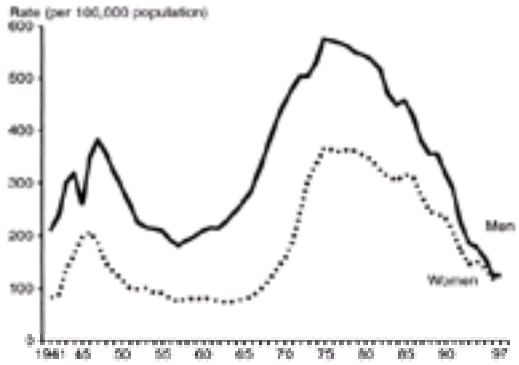


FIGURE 7.1. Trends in incidence of reported gonorrhea by gender, United States, 1941–1997. (From Aral SO, Holmes KK. Social and behavioral determinants of the epidemiology of STDs: industrialized and developing countries. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually transmitted diseases.* New York: McGraw-Hill, 1999:39–76, with permission.)

Humans are the only natural host for *N. gonorrhoeae.* Because the organism has a predilection for columnar or pseudostratified epithelium, mucous membranes that are lined by columnar, cuboidal, or noncornified squamous epithelial cells are most susceptible to infection with *N. gonorrhoeae* in adults (2). As a result, gonococcal infection is most commonly found in the urogenital tract (3). *N. gonorrhoeae* is a fastidious organism with specific nutrient and environmental needs. Its growth is optimal at a pH level of 7.4, a temperature of 35.5°C, and a 2% to 10% CO_2 atmosphere. Over the past 30 years, there has been a phenomenal expansion in our understanding of the pathogenic mechanisms of the gonococcus (4,5). The first step in this process was the work of Kellogg et al. (6), who demonstrated that there are differences in the virulence of *N. gonorrhoeae* associated with specific colony types. Of the Kellogg colony types, only types 1 and 2 (now called P+ colonies), which contain pili, are capable of producing infection, whereas types 3 and 4 (now called P- colonies), which do not contain pili, fail to cause infection (6). The pili appear to facilitate attachment of gonococci to epithelial surfaces (7,8). Other gonococcal surface structures in addition to pili are associated with pathogenesis.

Meyer (5) noted that pathogenic neisseriae persist in the host organism because of their ability to adapt to the host. This reflects the extraordinary capability pathogenic neisseriae possess to vary their surface structures. Not only is this property used to protect the organism from the host immune response, but such variation also affects the function of factors that interact with host cells. As a result, the gonococcus can interact with epithelial cells or phagocytic cells, adhere to cells, invade cells, or remain protected from serum factors inside a capsule of sialated lipopolysaccharide (5). These surface structures and functions are determined by proteins present in the outer membrane of the gonococcus. The most prominent protein in the outer membrane is the porins protein (Por), which was previously designated protein I (4). Por is an important cofactor in gonococcal invasion of epithelial mucosa cells (5) and is involved in the events leading to endocytosis of the gonococcus by mucosal cells (9). The opacity-associated proteins designated Opa (formerly protein II) comprise a family of proteins that promote cell adhesion, thus setting the stage for cell invasion

(4,5,10). The Opa proteins are the determinant of colony phenotype, a characteristic first noted by James and Swanson (11) to be important in the pathogenesis of gonococcal infection. They reported that transparent colonies (now known to be Opa-negative) are more characteristic in cultures from the endocervix than from the male urethra, particularly at the time of menses (11). Draper et al. (12) noted that transparent (Opa-negative) colonies were the virulent form recovered from the fallopian tubes of patients with laparoscopically confirmed PID. Colonies of *N. gonorrhoeae* containing Opa proteins (Opa-positive) appear opaque. Kupsch et al. (13) have shown that one Opa protein (Opa_{50}) interacts with epithelial cell lines and promotes invasion, whereas the ten remaining Opa proteins (Opa_{52}) mediate binding to phagocytic cells. All pathogenic neisseriae contain a reduction modifiable protein (RMP), which was formerly designated protein III (4). RMP is important in gonococcal pathogenesis because many blocking antibodies that prevent bactericidal activity are directed against this antigen (4). Thus, anti-RMP antibodies block access of other antibodies, including bactericidal immunoglobulin M (IgM), to their targets on the lipooligosaccharides on the gonococcal surface. Recent work by Rice et al. (14) demonstrated that RMP is important for successful transmission of *N. gonorrhoeae* to sexual partners. The mechanism for this finding is that anti-RMP antibodies in genital secretions block the usually protective antibodies present in genital secretions (4).

Additional gonococcal virulence factors include (a) lipopolysaccharides, which possess endotoxin activity, causing cytotoxic effects on the epithelium of the fallopian tube and the systemic findings of fever and toxicity (15); (b) immunoglobulin A (IgA) protease, which is present in all gonococci and destroys the secretory IgA (4,16); and (c) iron-repressible proteins, which are involved in uptake of iron, an essential requirement for growth of gonococci (4). Table 7.7 summarizes gonococcal structures involved in pathogenesis.

Structure	Function in Pathogenesis
Porin protein (Por)	(1) Insertion into host cell membranes Target for bactericidal, opsonic antibodies
Opacity-associated	Adherence protein (Opa)
Reduction modifiable protein	Target for blocking antibodies
Pili	Adherence
Lipooligosaccharide	Tissue toxin Target for bactericidal, chemotactic antibodies
Iron-repressible proteins	Iron uptake from transferrin, lactoferrin, hemoglobin
Immunoglobulin A (IgA), protease	(1) escape from mucosal IgA
Peptidoglycan	Tissue toxin

TABLE 7.7. STRUCTURES OF *Neisseria gonorrhoeae* INVOLVED IN PATHOGENESIS

As with other infections, the initial step in gonococcal infection is adherence of *N. gonorrhoeae* to mucosal cells lining the genitourinary tract. This process of adherence is mediated by pili and other surface proteins (8,17). This step is followed by a process of pinocytosis by which the organism is transported into epithelial cells

and then into submucosal tissues (9). Attachment of *N. gonorrhoeae* also results in the release of the endotoxin gonococcal lipopolysaccharide, which damages the ciliated-nonciliated cells of the fallopian tube epithelium (15,18).

Among nonpregnant women, *N. gonorrhoeae* is an important cause of urethritis, cervicitis, and PID (19,20). Pharyngeal gonorrhea and disseminated gonorrhea occur in men and women. Infection with *N. gonorrhoeae* in pregnancy is also a major concern. Gonorrheal ophthalmia neonatorum has long been recognized as a major consequence of maternal infection. More recently, an association between maternal gonococcal infection and disseminated gonococcal infection (DGI), amniotic infection syndrome, and perinatal complications such as premature ruptured membranes, chorioamnionitis, prematurity, intrauterine growth retardation, neonatal sepsis, and postpartum endometritis has been recognized.

Epidemiology

The current epidemic of gonorrhea commenced in 1957 and reached its peak in 1975, at 473 cases per 100,000, a nearly 300% increase in gonorrhea cases between 1966 and 1975. Since then, gonorrhea rates have leveled and have begun to decline at a progressively increased rate (1,2,21) (Fig. 7.1). Thus, in 1984, the rate was 324 cases per 100,000; in 1991, 247 per 100,000; in 1995, 149 per 100,000; and in 1997, 122 per 100,000—the lowest rate of reported gonorrhea infection in the United States since the beginning of World War II (21). However, in 1998, the rate increased for the first time since 1985, reaching 132.9 cases per 100,000, an 8.9% increase (1). Similarly the number of reported cases of gonorrhea decreased from more than 1 million in 1976 to 355,642 in 1998.

Several important changes in the epidemiology of gonorrhea in the United States have taken place during this decline (2,21). Whereas in 1987, twice as many cases were reported from public STD clinics than from private providers, by 1996 only slightly more than one half of reported gonorrhea cases were from STD clinics (21). For women, this pattern is even more dramatic, with nearly two thirds of gonorrhea cases reported from non-STD clinical sites. In 1966, the male to female ratio of gonorrhea cases was 3 : 1. This ratio has declined rapidly, and by 1996 the male to female ratio was 1 : 1 (21).

In the United States, there is a dramatic variance in the incidence and trends in incidence of reported gonorrhea cases among different racial groups (1,2,21,22). As of 1996, the incidence in Black non-Hispanics was 826 per 100,000, compared with 106 for American Indian/Alaskan natives, 69 for Hispanics, 26 for White non-Hispanics, and 18.6 for Asian/Pacific Islanders. In the United States, the highest age-, gender-, and race ethnicity-adjusted rates for gonorrhea are in 15- to 19-year-old African American non-Hispanics, with a 1996 reported gonorrhea incidence of 3,791 per 100,000 (22). Another important determinant of the incidence of gonorrhea is age. Hook and Hansfield (2) reported that 77% of reported cases of gonorrhea in the United States in 1995 were among persons aged 15 to 29 years, with the highest rates occurring in the 15- to 19-year-old age-group. If only sexually active women are considered, the incidence of gonorrhea is twice as high in adolescents than in women aged 20 to 24 years (2,23,24).

Additional risk factors for gonorrhea include low socioeconomic status, early onset of sexual activity, unmarried marital status, a past history of gonorrhea, illicit drug

abuse, and prostitution (2,25,26 and 27). Recently, Zaidi et al. (28) reported that in urban centers in the United States, six factors accounted for 75% of the variation in gonorrhea morbidity in these cities. These factors were (a) population density, (b) percentage of households with female heads, (c) city government general expenditure per capita, (d) violent crime rate, (e) percentage of families below poverty level, and (f) percentage of births to mothers younger than 20 years.

Transmission of gonorrhea is almost entirely by sexual contact. The woman is at greater risk of infection than the man. Although it is estimated that a man having a single sexual encounter with a gonorrhea-infected woman will become infected 20% to 25% of the time, the risk of transmission from man to woman is estimated at 50% to 90% (29,30 and 31). A short incubation time of 3 to 5 days occurs.

As noted by Hook and Handsfield (2), the prevalence of gonorrhea in a community is dynamic, fluctuates over time, and is influenced by a number of factors, which are interactive. Mathematical models have been developed that suggest that the prevalence of gonorrhea is sustained by both continued transmission by asymptomatically infected individuals and “core group” transmitters who are more likely to acquire and transmit gonorrhea than the general population (32,33 and 34). Current opinion holds that this core group provides the major impetus for continued endemicity of gonorrhea and thus should be the target of screening and prevention efforts. The core group is mainly characterized by residence within inner cities and low socioeconomic status. However, it also includes individuals with repeated episodes of gonorrhea, persons who do not abstain from sex in the face of symptoms or exposure to *N. gonorrhoeae,* and those who practice high-risk behavior such as prostitution, patronizing prostitutes, or illicit drug abuse (2,21).

Clinical Presentation

N. gonorrhoeae infects men and women. In adults, the gonococcus attaches to nonsquamous epithelium–lined mucosal membranes; thus, the primary site of involvement is the genitourinary tract. In men, the infection is usually an acute symptomatic urethritis. Female infection is often asymptomatic, and the primary site of involvement is the endocervical canal and the transition zone of the cervix. However, it has become apparent that women with endocervical gonorrhea frequently are symptomatic, and most commonly present with symptoms such as vaginal discharge, dysuria, and abnormal uterine bleeding (2,35). Urethral colonization occurs in most women with endocervical gonorrhea, and infection of the periurethral (Skene) glands, Bartholin glands, and anorectum also occurs.

Clinical Manifestations of Uncomplicated Anogenital Gonorrhea in Women

Uncomplicated anogenital gonorrhea in women may involve the endocervix, urethra, Skene glands, Bartholin glands, or the anus. The most commonly infected site is the endocervix. Gonococcal infection of the vagina is rare, except in prepubertal and postmenopausal patients. Urethral colonization is present in 70% to 90% of women infected with *N. gonorrhoeae* (36,37). The rectum is infected in 35% to 50% of women with endocervical gonococcal infection and is the only site of infection in approximately 5% of women (35,36,37,38,39 and 40). Unlike in men, anal gonorrhea in women is often asymptomatic. If present, symptoms of anorectal gonorrhea range from mild pruritus and mucoid discharge to severe proctitis symptoms. Whereas 10% to 20% of heterosexual women with urogenital gonorrhea have coexistent

pharyngeal gonorrhea, the pharynx is the sole site in less than 5% of women (41). Fellatio carries a higher risk for acquisition of *N. gonorrhoeae* than cunnilingus (42). Most patients with pharyngeal gonorrhea are asymptomatic. In those with symptomatic infection, a mild sore throat and erythema are present. However, oral ulcerative lesions and exudate of the pharynx and tonsils may occur.

At one time, uncomplicated anogenital gonorrhea in women was considered an asymptomatic disease. It is now recognized that although most women harboring *N. gonorrhoeae* are asymptomatic, many women with anogenital gonorrhea are symptomatic. Common symptoms include vaginal discharge, dysuria, intermenstrual bleeding, menorrhagia, and pelvic discomfort. Curran et al. (35) reported that positive gonococcal cultures were obtained at a higher rate from women with symptoms or signs of genital tract disease. Similarly, Weisner (42) suggested that between 40% and 60% of women who have gonorrhea develop some symptoms. It is unclear what the incubation period for urogenital gonorrhea in women is, but those who develop symptomatic gonococcal infection do so within 10 days (43,44). In 15% to 20% of women with uncomplicated anogenital gonorrhea, upper genital tract infection (i.e., PID) occurs (20). Gonococcal-associated PID tends to occur at the end of or just after menstruation. A detailed description of PID and the role of *N. gonorrhoeae* in its etiology and pathogenesis are reviewed in Chapter 14 (Pelvic Inflammatory Disease).

The cervix infected with *N. gonorrhoeae* can appear healthy or reveal an inflamed cervical canal with ectopy and a mucopurulent exudate. The area of ectopy is edematous, erythematous, and friable. In general, these signs of gonococcal cervicitis are indistinguishable from other causes of cervicitis, so an absolute diagnosis of gonococcal cervicitis requires confirmatory laboratory tests. Gonococcal infection of the urethra, Skene glands, or Bartholin glands may be associated with mucopurulent exudate, which can be expressed from these structures.

Gonococcal infections in pregnant patients are most commonly asymptomatic. The two most common symptoms are vaginal discharge and dysuria. On examination, endocervicitis may be present with erythema and a mucopurulent discharge. If routine screening for *N. gonorrhoeae* is not employed during pelvic examinations, the presence of lower genital tract complaints or signs such as abnormal bleeding, discharge, dysuria, mucopurulent endocervicitis, or pelvic discomfort should suggest that cultures be obtained to determine whether the gonococcus is present.

Nongenital Gonococcal Syndromes

Nongenital tract gonococcal disease may result from direct or contiguous spread and by bloodstream dissemination. Direct or contiguous spread occurs for PID, anorectal infection, perihepatitis (Fitz-Hugh and Curtis syndrome), conjunctivitis, and pharyngeal gonococcal infection.

Rarely, *N. gonorrhoeae* causes conjunctivitis in adults. This usually is a direct result of sexual contact or an indirect result via contaminated hands, amniotic fluid at delivery, or accidental inoculation in the laboratory with clinical isolates. The typical presentation for gonococcal conjunctivitis is an acute onset of purulent conjunctivitis with extensive inflammation and copious purulent secretions.

Acute PID is a local complication of gonorrhea and is the most common complication of gonorrhea in women, occurring in an estimated 10% to 20% of untreated cases (20). Bartholin gland abscess is the next most frequent complication of gonococcal infection in women.

Disseminated Gonococcal Infections

DGI, the most common systemic complication of gonorrhea, occurs when gonococcal bacteremia produces extragenital manifestations of gonococcal infection. The prevalence of DGI among total gonorrhea cases ranges from 0.1% to 0.3%, with women predominating over men by about 4 : 1 (45,46). Rates of up to 3% have been reported in high-prevalence populations (2). Most women with DGI develop symptoms either during pregnancy, particularly in the third trimester, or within 7 days from the onset of menstruation. Only certain strains of *N. gonorrhoeae* have a predisposition to disseminate. In general, they are strains that are highly sensitive to antibiotics (47), are resistant to bactericidal activity of human serum (48), and have a unique nutritional requirement for arginine, hypoxanthine, and uracil (49). In addition, complement deficiencies have been demonstrated to be associated with an increased risk for DGI (50).

Patients are considered to have proven DGI if they have positive cultures from blood, joint fluid, skin lesions, or otherwise sterile sources (2). This group makes up less than 50% of DGI cases (45). Probable DGI is defined when *N. gonorrhoeae* can be cultured from the primary site in the lower genital tract or pharynx or in a sexual partner. Patients with a clinical syndrome consistent with DGI and an appropriate clinical response to treatment but in whom all culture sites are negative for *N. gonorrhoeae* are considered to have possible DGI (2).

DGI manifests two stages: an early bacteremia stage and a late stage (Table 7.8). The bacteremia stage is characterized by chills, fever, typical skin lesions, and asymmetric joint involvement. Blood cultures are positive for *N. gonorrhoeae* in half of the patients cultured during the bacteremia stage. The bacteremia stage is associated with a dermatitis that is characterized by various skin lesions due to gonococcal emboli and occurs in 50% to 75% of cases (51). These lesions appear initially as small vesicles that become pustules and develop a hemorrhagic base. The center becomes necrotic. These lesions occur on any body region but are most frequently present on the volar aspects of the upper extremities, the hands, and the fingers. These skin lesions resolve spontaneously without residual scarring.

Early stage
Migratory arthritis
Tenosynovitis
Dermatitis
Late stage
Arthritis
Perihepatitis
Osteomyelitis
Pericarditis
Endocarditis
Meningitis

TABLE 7.8. CLINICAL MANIFESTATIONS OF DISSEMINATED GONOCOCCAL INFECTION

Joint symptoms are frequently present during the early stage, with arthritis developing in 30% to 40% of cases (2,51). Asymmetric joint involvement is the usual pattern, most often affecting the knee, elbow, wrist, ankle, and metacarpophalangeal joints. The arthritis is migratory (i.e., one joint heals as another becomes affected). In two thirds of patients, tenosynovitis is present (51). The most frequent sites are the dorsal tendons of the hands, wrists, and ankles.

The late stage of DGI is characterized by frank arthritis with permanent joint damage, endocarditis, meningitis, pericarditis, osteomyelitis, and perihepatitis (2,51). With arthritis, the knees, ankles, and wrist joints are the sites most commonly involved. Since the introduction of penicillin, gonococcal endocarditis and meningitis have been rarely seen complications of DGI. It is estimated that gonococcal endocarditis occurs in 1% to 3% of patients with DGI. However, recognition of gonococcal endocarditis is crucial because there is rapidly progressive valvular damage, particularly to the aortic valve (2). Whereas DGI is more common in women, gonococcal endocarditis is more common in men. Typically, patients present with a febrile illness of several weeks' duration in association with malaise, fatigue, and weight loss (51). Regurgitant murmurs are almost always present, with echocardiography demonstrating valvular vegetations or flail leaflets (51).

Neonatal Gonococcal Ophthalmia

Gonococcal ophthalmia neonatorum has been recognized since 1881. Before the introduction of the Credé method of silver nitrate prophylaxis, ophthalmia neonatorum occurred in approximately 10% of infants born in the United States. Introduction of eye prophylaxis resulted in a rapid reduction in this rate. However, the resurgence of gonorrhea during the 1960s and 1970s led to a reappearance of gonococcal conjunctivitis in newborns, which is the most common clinical manifestation of *N. gonorrhoeae* in the newborn. Gutman (52) has reported that 30% to 35% of exposed neonates acquire *N. gonorrhoeae* during vaginal delivery from infected mothers.

Most newborns who are infected with gonorrhea acquire it during passage through an infected cervical canal. Gonococcal ophthalmia usually is manifested within 4 days of birth, but incubation periods of up to 21 days have been reported. A frank purulent conjunctivitis occurs, which usually affects both eyes. Untreated gonococcal ophthalmia can rapidly progress to corneal ulceration, resulting in corneal scarring and blindness.

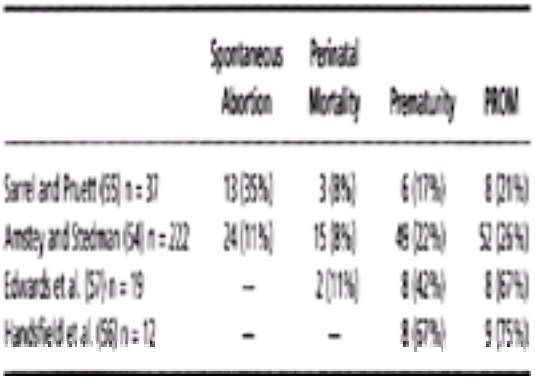
Gonococcal Infection in Pregnancy and the Neonate

Postabortal gonococcal endometritis and salpingitis are now well-recognized complications of postpregnancy termination. Patients undergoing therapeutic abortion who have untreated endocervical gonorrhea are at increased risk for

developing postabortion endometritis (53).

Although the problem of gonococcal ophthalmia neonatorum has been addressed for more than 100 years, the effects of gonorrheal infection on both mother and fetus were not fully appreciated until 30 years ago (54,55,56 and 57). The amniotic infection syndrome is a manifestation of gonococcal infection in pregnancy. This entity presents with placental, fetal membrane, and umbilical cord inflammation, which occurs after PROM (premature rupture of the membranes) and is associated with positive oral gastric aspirate for *N. gonorrhoeae,* leukocytosis, neonatal infection, and maternal fever. This syndrome is characterized by PROM, premature delivery, and a high infant morbidity or mortality rate.

Table 7.9 summarizes studies demonstrating an association between untreated maternal endocervical gonorrhea and perinatal complications, including an increased incidence of PROM, preterm delivery, chorioamnionitis, neonatal sepsis, and maternal postpartum sepsis (54,55,56 and 57). In addition, a higher incidence of intrauterine growth retardation has been observed in gravid women with gonococcal infection.



	Spontaneous Abortion	Perinatal Mortality	Prematurity	PROM
Sarrel and Pruett (55) n = 37	13 (35%)	3 (8%)	6 (17%)	8 (21%)
Amstey and Steadman (54) n = 222	24 (11%)	15 (8%)	49 (22%)	52 (25%)
Edwards et al. (57) n = 19	–	2 (11%)	8 (42%)	8 (67%)
Handsfield et al. (56) n = 12	–	–	8 (67%)	9 (75%)

TABLE 7.9. IMPACT OF UNTREATED GONORRHEA ON PERINATAL OUTCOME

Amstey and Steadman (54) noted that women from whom *N. gonorrhoeae* was recovered (even if treated before delivery) were significantly more likely to have PROM and preterm delivery. Sarrel and Pruett (55) reported high rates of septic spontaneous abortion (35%) and PROM (22%) in pregnant women with symptomatic gonococcal infection. Handsfield et al. (56) demonstrated that maternal gonococcal infection in the third trimester was associated with an increased risk for PROM, prematurity, chorioamnionitis, fetal infection, neonatal sepsis, and maternal infection postpartum. Similarly, Edwards et al. (57) demonstrated that *N. gonorrhoeae*–positive pregnant women had an increased incidence of chorioamnionitis, perinatal infections, and intrauterine growth retardation. Such investigations demonstrate the need to screen pregnant women (particularly among populations at high risk for STDs) for *N. gonorrhoeae.* Because almost all patients with gonococcal infection during pregnancy are asymptomatic, we recommend routine cultures for *N. gonorrhoeae* at the initial prenatal visit and repeat the culture early in the third trimester. Alternatively, in settings with a low prevalence of

gonorrhea, screening may be limited to those patients deemed at high risk for gonococcal infection (e.g., those with multiple sex partners or other STDs, adolescents, and those with previous gonorrhea or symptoms suggestive of gonorrhea).

Diagnosis

The laboratory diagnosis of infection with *N. gonorrhoeae* requires identification of the organism at infected sites. Methods available include Gram stains, cultures, immunochemical detection, or molecular diagnostic techniques.

In men with urethral discharge and dysuria, the Gram stain of the urethral exudate is considered diagnostic for *N. gonorrhoeae* when Gram-negative diplococci are seen within or closely associated with polymorphonuclear leukocytes (58). However, most women with gonorrhea (pregnant and nonpregnant) are asymptomatic. Thus, the diagnosis of these infections depends on sampling potentially infected sites. The major site of primary infection in women is the endocervix, although the anal canal, urethra, and pharyngeal cavity are important sites to consider as well. Unfortunately, microscopic examination of a Gram-stained specimen from the endocervix in asymptomatic women produces a diagnosis of gonorrhea in only 60% of women, compared with 95% of men (Table 7.10). Although smears from the endocervix are less sensitive than those from the male urethra, a smear positive for gonorrhea is highly specific when examined by experienced individuals, particularly when obtained from symptomatic women with mucopurulent cervicitis or PID (2).

	Sensitivity	Specificity
Men (urethra)		
Symptomatic urethritis	90–95%	95–100%
Asymptomatic	50–70%	95–100%
Women (endocervix)		
Uncomplicated gonorrhea	50–70%	95–100%
Pelvic inflammatory disease	60–70%	95–100%
Anorectum	40–60%	95–100%
Blind swabs		

Source: From Hook EW, Handsfield HH. Gonococcal infections in adults. In: Holmes KK, Sparling PF, Mardh P-A, et al., eds. Sexually transmitted diseases. New York: McGraw-Hill, 1999:451–466, with permission.

TABLE 7.10. USE OF GRAM STAIN IN DIAGNOSIS OF LOWER GENITAL TRACT GONORRHEA

In women, the diagnosis of *N. gonorrhoeae* infection requires isolation of the organism by culture. Ideally, all sexually active women should be screened at every opportunity (i.e., annual routine pelvic examinations, presenting with gynecologic complaints). Obviously, this would be a major logistic and economic burden, particularly in patient populations with low rates (less than 1%) of gonorrhea. At a minimum, certain at-risk patient groups should be routinely screened. These include partners of men with gonorrhea or urethritis, women with symptoms and signs

referred to the lower genital tract, patients with known other STDs, patients with multiple sexual partners, and patients with PID. Phillips et al. (59) attempted to determine clinical factors that would identify women at risk for gonococcal infection. Factors associated with gonococcal cervical infection included the following: sexual contact with a partner who may have had gonorrhea or urethral discharge in the past 3 months, bleeding induced by cervical swab, method of payment (Medicaid), 16 years or younger at first intercourse, and lower abdominal or pelvic pain. Of the patients with three or more risk factors, 10% had *N. gonorrhoeae* infection. With more than one risk factor, 2.5% were culture positive for *N. gonorrhoeae.* The incidence of *N. gonorrhoeae* was 0.2% in the group with none of the risk factors. At least high-risk, if not all, pregnant women should have a culture for *N. gonorrhoeae* obtained during their initial prenatal visit. In patients at high risk for gonorrheal infection, cultures should be repeated in the third trimester.

Clinical isolation is best performed using a selective media for *N. gonorrhoeae,* such as Thayer-Martin medium containing the antibiotics vancomycin, colistin, and nystatin, which inhibit the growth of contaminating organisms present in the same body sites as the gonococcus. The proper collection, handling, and processing of culture specimens are crucial to obtaining accurate results. *N. gonorrhoeae* organisms do not tolerate drying and thus require immediate inoculation on appropriate media and placement in an incubator. Ideal growth occurs at 35°C to 37°C in a 5% $C0_2$ atmosphere. A dry, sterile cotton-tipped swab is inserted into the endocervical canal, moved from side to side, and allowed to remain for 15 to 30 seconds for absorption of organisms to the swab. The specimen is then plated onto selective media for *Neisseria* sp (i.e., Thayer-Martin or New York City). After inoculation, this media should be placed in a carbon dioxide incubator or candle jar to provide an adequate concentration of carbon dioxide. A modification of this medium is the addition of trimethoprim to prevent *Proteus* contamination. When culture facilities are not readily available, a holding or transport medium should be used. Goodhart et al. (60) reviewed the results with these various systems. Transport via holding media such as that of Aime, Culturette, or Stuart was associated with a 10% to 79% loss of isolates after 24 hours. Use of an environmental chamber (JEMBEC) for transport led to 7% to 22% loss of isolates after 1 day, and 4% to 55% loss after 3 days (i.e., over a weekend). Transgrow medium is a modification of the Thayer-Martin selective medium, which is available to clinicians in a bottle sealed under carbon dioxide tension. After inoculation of the specimen onto the Transgrow medium, the bottle is resealed and transported (or mailed) to an appropriate laboratory. However, delays in transport significantly decrease the reliability of this system, and in general, Transgrow medium has not proven to be practical.

The diagnosis of *N. gonorrhoeae* infection is made by identification of the organism with a typical growth on selective media, a positive oxidase reaction, and a Gram-negative diplococcal morphology on a Gram stain of the isolated colonies. Fermentation reactions may also be performed. They take advantage of the ability of the gonococcus to ferment glucose, but not sucrose or maltose. Because of the spread of antibiotic-resistant *N. gonorrhoeae,* all gonorrhea cases should be confirmed or diagnosed by culture to allow for antimicrobial susceptibility testing.

In women, a single endocervical culture on selective media will detect 80% to 90% of uncomplicated anogenital gonorrhea (36,61,62). *N. gonorrhoeae* can be isolated from the anal canal in 35% to 50% of women with gonococcal infection and this is the only infected site in up to 5% of women with gonorrhea (36,39,61). *N. gonorrhoeae* is

recovered from the pharynx in 5% to 20% of women with gonorrhea, but this is the only site of infection in less than 5% (36,41,61). The urethra, Bartholin ducts, and Skene glands are rarely the sole site of infection and thus not usually cultured (2).

For optimal yield in culturing of *N. gonorrhoeae,* either two consecutive endocervical specimens or a combination of an endocervical and an anal specimen should be obtained. A single endocervical swab will miss approximately 10% of gonococcal infection. Gonococcal pharyngitis is more frequently encountered in women. Although these cases often present with clinical symptoms similar to those of other types of pharyngitis, the disease may be asymptomatic. In patients with sore throat or with a history of oral genital contact, cultures should be obtained from the tonsillar area and from the pharynx behind the uvula. The limitations of the Gram stain and the time delay associated with culture for *N. gonorrhoeae* have led to a search for methods to provide rapid and accurate diagnosis of *N. gonorrhoeae* infection. Serodiagnosis for gonorrhea has been disappointing because of persistence of antibody due to previous gonococcal disease. The Gonozyme test is a solid-phase enzyme immunoassay for detecting gonococcal antigens in urethral or endocervical specimens (63). Although this test has high sensitivity and specificity in symptomatic men, the lower sensitivity and specificity for diagnosis of cervical infections precludes its use as a screening test for low-prevalence women.

Reliable nonculture assays for detection of gonorrhea have recently become available and have gained increasing acceptance (2). Hook and Handsfield suggested that the use of these new nonculture assays will continue to increase because of their satisfactory performance, extensive promotion by manufactures, and because specimens used by those assays for gonorrhea can also often be used to test for *C. trachomatis* (2). The first widely accepted of these techniques was nonamplified DNA probe tests (e.g., PACE 2 system by Gen-Probe). Currently nonamplified DNA probes are the most commonly used nonculture method for diagnosis of gonorrhea in the United States (2). This test uses a single-stranded DNA probe, which hybridizes to ribosomal RNA of *N. gonorrhoeae.* Studies have demonstrated that nonamplified DNA probes have sensitivity ranging from 89% to 97% and a specificity of 99%. Thus, they compare favorably to culture with selective media and often in cost (64,65 and 66).

More recently, nucleic acid amplification technologies have been introduced for detection of *N. gonorrhoeae.* These techniques include ligase chain reaction (LCR), polymerase chain reaction (PCR), and transcription-mediated amplification. LCR is the first amplified nucleic acid test available in the United States for diagnosis of gonorrhea. LCR has been shown to a have sensitivity ranging from 95% to 98%, which is equal to that seen with culture on selective media (67,68). LCR is equally sensitive when used on first-void urine specimens for detection of *N. gonorrhoeae* in men and women (68). This latter attribute provides an opportunity for screening women and men in lieu of pelvic or genital examinations (2). Even more useful in women is the use of vaginal swab specimens for PCR or LCR (69).

Treatment

Uncomplicated Gonorrhea

The choice of antimicrobial agents for the treatment of gonococcal infection to a large extent reflects *in vitro* resistance patterns to *N. gonorrhoeae.* Additional factors

that influence the choice of antimicrobial agents include maximizing compliance with single-dose (observed) therapy and the probability that patients infected with *N. gonorrhoeae* are coinfected with other STDs (particularly *C. trachomatis*) (2).

Although most *N. gonorrhoeae* are sensitive to many antimicrobial agents including penicillins, tetracyclines, macrolides, cephalosporins, erythromycin, aminoglycosides, aminocyclitols, and quinolones (70), increasing resistant strains have appeared (71,72,73,74 and 75). Sulfonamide, the first effective therapy for gonorrhea, became available in the mid-1930s. By 1944 Sulfamide resistance had become prevalent and gonococcal infection persisted in approximately one third of patients treated with maximal doses of sulfonamide (2).

Once penicillin was available after World War II, it became the drug of choice for gonorrhea. Despite a progressive increase in resistance by *N. gonorrhoeae,* penicillins remained the therapy of choice by increasing the dose of penicillin and coadministering probenecid (2). Similar patterns of progressive increased resistance was seen with tetracycline and erythromycin. However, in 1976 strains of *N. gonorrhoeae* infection with high-level penicillin resistance due to plasmid-mediated production of b-lactamase were initially reported (76).

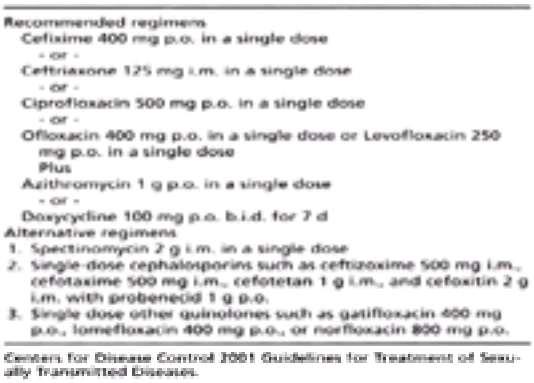
Since their identification in 1976, penicillinase-producing *N. gonorrhoeae* (PPNG) strains have steadily increased in frequency in the United States. From the 190 cases in 1977, the number of reported PPNG cases rose to more than 40,000 in 1988 (2). Thus, more than 4% of reported cases of gonorrhea were due to PPNG strains. By 1991, sentinel surveillance data suggested that 13% of gonococcal isolates were PPNG (75). The highest levels of PPNG isolates occur in southern Florida, New York City, and California.

In addition to the plasmid-mediated production of b-lactamase enzyme associated with PPNG, two other resistant strains of *N. gonorrhoeae* have emerged in the United States (71). Gonococcal strains with high-level chromosomal resistance to penicillin (i.e., chromosomal-resistant *N. gonorrhoeae* [CMRNG]) were first identified in 1983 in North Carolina. By 1987 the CDC, based on a nationwide antimicrobial resistance surveillance program, reported that CMRNG form of resistance had become quite common (72). This chromosomally mediated resistance also includes resistance to tetracycline, cephalosporins, spectinomycin, and aminoglycosides. More recently, gonococcal isolates with plasmid-mediated, high-level resistance to tetracycline (i.e., tetracycline-resistant *N. gonorrhoeae* [TRNG]) have been reported. The TRNG strains owe their resistance to acquisition of a *tet* M gene that codes for high-level tetracycline resistance (72,73 and 74). TRNG strains have been detected throughout the United States with the highest levels reported from the northeastern area, particularly in Baltimore where they made up to 15% to 20% of *N. gonorrhoeae* isolates (73 and 74). More recently, the emergence of fluoroquinolone resistance has been demonstrated (77,78).

In the Gonococcal Isolate Surveillance Project of the CDC, more than 35,000 isolates of *N. gonorrhoeae* underwent susceptibility testing from 1988 to 1994 (77). In 1994, 30.5% of isolates had chromosomally or plasmic-mediated resistance to penicillin or tetracycline, with 15.6% and 21.7% of gonococcal isolates resistant to penicillin and tetracycline, respectively (77). Most isolates (99.9%) were highly susceptible to broad-spectrum cephalosporins. Decreased susceptibility to ciprofloxacin was seen in 0.4% of 1991 isolates, increasing to 1.3% of isolates in

1994 (77). Four isolates were resistant to ciprofloxacin (78).

The guidelines for treatment of uncomplicated and complicated gonococcal disease have been recently updated (1998) by the CDC (70). Both men and nonpregnant women with uncomplicated gonococcal infection are treated with the same drug regimens (Table 7.11). In clinical trials, the regimens recommended by the CDC in the 1998 STD treatment guidelines (70) have demonstrated cure rates of more than 95% in the treatment of uncomplicated anogenital gonorrhea. Ceftriaxone (in a single injection of 125 mg) results in sustained high bactericidal blood levels and has been shown to be effective and safe for the treatment of uncomplicated gonorrhea at all sites (70). The CDC notes that ceftriaxone cures 99.1% of uncomplicated urogenital and anogenital gonorrhea (70). The disadvantages of ceftriaxone is that it is expensive and must be administered by injection. Ceftriaxone is also effective against incubating syphilis.



Recommended regimens
Cefixime 400 mg p.o. in a single dose
- or -
Ceftriaxone 125 mg i.m. in a single dose
- or -
Ciprofloxacin 500 mg p.o. in a single dose
- or -
Ofloxacin 400 mg p.o. in a single dose or Levofloxacin 250 mg p.o. in a single dose
Plus
Azithromycin 1 g p.o. in a single dose
- or -
Doxycycline 100 mg p.o. b.i.d. for 7 d
Alternative regimens
1. Spectinomycin 2 g i.m. in a single dose
2. Single-dose cephalosporins such as ceftizoxime 500 mg i.m., cefotaxime 500 mg i.m., cefotetan 1 g i.m., and cefoxitin 2 g i.m. with probenecid 1 g p.o.
3. Single dose other quinolones such as gatifloxacin 400 mg p.o., lomefloxacin 400 mg p.o., or norfloxacin 800 mg p.o.

Centers for Disease Control 2001 Guidelines for Treatment of Sexually Transmitted Diseases.

TABLE 7.11. CENTERS FOR DISEASE CONTROL RECOMMENDED TREATMENT OF UNCOMPLICATED GONOCOCCAL INFECTIONS OF THE CERVIX, URETHRA, AND RECTUM IN ADULTS (2001)

Cefixime's antimicrobial spectrum is similar to that of ceftriaxone. However, the 400-mg dose does not provide as high or as sustained a bactericidal level as ceftriaxone (70). No gonococcal strains resistant to cefixime have been reported, and in clinical trials, cefixime as a single 400-mg oral dose curved more than 97% of uncomplicated gonococcal infections (70). The major advantage of cefixime is its oral administration.

Ciprofloxacin at a dose of 500 mg orally provides sustained bactericidal levels against *N. gonorrhoeae* in the blood (70). Clinical trials have demonstrated it to be effective and safe, with cure rates of 99.8% noted (70). Ofloxacin (400 mg) is also safe and effective for treatment of uncomplicated gonorrhea, curing 98.4% of infections (70). Until recently, no resistant strains of *N. gonorrhoeae* to fluoroquinolones had been reported in the United States. Before May 1994, the CDC reported that since 1992, gonococcal strains with decreased susceptibilities to ciprofloxacin had been isolated sporadically from patients in the United States through the Gonococcal Isolate Surveillance Project (78). However, in May 1994, the CDC reported the emergence of fluoroquinolone resistance from Ohio and Hawaii

(78). As noted previously, decreased susceptibility to ciprofloxacin was present in 63% of gonococcal isolates in the Gonococcal Isolate Surveillance Project (77). As of 1998, the CDC felt that clinically important quinolone resistance was still uncommon in the United States and did not justify changes in the recommendations of fluoroquinolones for routine treatment of uncomplicated gonorrhea (70). Providers using fluoroquinolones to treat gonorrhea should monitor susceptibility patterns to these agents (70). It has been suggested that increasing fluoroquinolone resistance may soon limit the effectiveness of these agents in the treatment of gonorrhea (2,77). Quinolones are contraindicated for pregnant or nursing women, and they are not active against syphilis.

Among the alternative regimens, spectinomycin is useful for treating patients who are allergic to or who cannot tolerate cephalosporins or quinolones. However, it is expensive, is injectable, is inactive against syphilis, and is relatively inactive against pharyngeal gonorrhea. In addition, strains of *N. gonorrhoeae* resistant to spectinomycin have been reported (70). None of the alternative injectable cephalosporins has any advantage over ceftriaxone or the widespread clinical experience of ceftriaxone. Among alternative quinolones, enoxacin, lomefloxacin, and norfloxacin appear to be effective and safe but do not offer any advantage over ciprofloxacin or ofloxacin.

Azithromycin (2 g orally as a single dose) is effective against uncomplicated gonococcal infection, but its cost and high rate of gastrointestinal tract distress preclude it from being recommended for treatment of gonorrhea (70). At the oral dose of 1 g, the gastrointestinal tract distress is reduced, but the efficacy of 93% is insufficient.

Concomitant infection with *C. trachomatis* is common in individuals infected with *N. gonorrhoeae* (2,70). Among women with gonorrhea, 20% to 30% are coinfected with chlamydia, and in men, there is a 10% to 20% rate of coinfection (2). Thus, the CDC recommends that all persons treated for gonorrhea should also be presumptively treated for chlamydial infection. Azithromycin (1 g orally in a single dose) or doxycycline (100 mg orally twice a day for 7 days) is the preferred regimen in nonpregnant individuals, although in pregnancy, an erythromycin regimen or amoxicillin should be used (Chapter 5, Chlamydial Infections).

Persons treated for gonorrhea should be screened for syphilis by serology. Regimens for treating gonorrhea that include ceftriaxone or a 7-day course of doxycycline or erythromycin probably cure incubating syphilis.

Pregnant or lactating women should not be treated with tetracycline or the quinolones. In pregnant women, *N. gonorrhoeae* should be treated with a recommended or alternative cephalosporin (70). In cases in which cephalosporins cannot be tolerated, spectinomycin (2 g intramuscularly) should be administered. Either erythromycin or amoxicillin is the recommended treatment for presumptive chlamydial infection in pregnancy.

Test of cure is no longer recommended for individuals with uncomplicated gonorrhea who received any of the CDC-recommended regimens for uncomplicated gonorrhea (70). Persons with persistent symptoms should undergo a subsequent culture and any *N. gonorrhoeae* recovered should be tested for antimicrobial susceptibility. Because patients infected with gonorrhea are at high risk for reinfection, repeated

screening 1 to 2 months after treatment is appropriate.

Sexual partners of patients with gonorrhea must be examined, must undergo a culture, and must be treated (before receiving the culture results). Treatment should be with one of the CDC regimens for uncomplicated gonorrhea, preferably with treatment for coexistent chlamydial infection.

Complicated Gonorrhea

Treatment of complicated (upper genital or extragenital) gonococcal infection depends on the anatomic location, the severity of the disease, and the clinical response. Basically, the antibiotics that are used for uncomplicated gonorrhea are used by complicated gonorrhea, but the doses are different.

Disseminated Gonorrhea

Ceftriaxone is the drug of choice for DGI. Patients allergic to penicillins and cephalosporins can be treated with spectinomycin (2 g intramuscularly every 12 hours). The current CDC recommendations and alternative drugs are listed in Table 7.12.

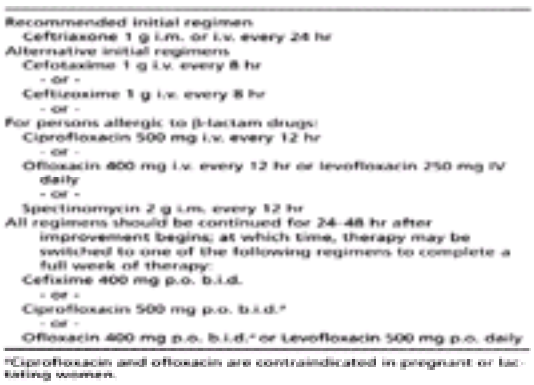

Recommended initial regimen
Ceftriaxone 1 g i.m. or i.v. every 24 hr
Alternative initial regimens
Cefotaxime 1 g i.v. every 8 hr
- or -
Ceftizoxime 1 g i.v. every 8 hr
- or -
For persons allergic to β-lactam drugs:
Ciprofloxacin 500 mg i.v. every 12 hr
- or -
Ofloxacin 400 mg i.v. every 12 hr or levofloxacin 250 mg IV daily
- or -
Spectinomycin 2 g i.m. every 12 hr
All regimens should be continued for 24–48 hr after improvement begins; at which time, therapy may be switched to one of the following regimens to complete a full week of therapy:
Cefixime 400 mg p.o. b.i.d.
- or -
Ciprofloxacin 500 mg p.o. b.i.d.*
- or -
Ofloxacin 400 mg p.o. b.i.d.* or Levofloxacin 500 mg p.o. daily
*Ciprofloxacin and ofloxacin are contraindicated in pregnant or lactating women.

TABLE 7.12. CENTERS FOR DISEASE CONTROL TREATMENT RECOMMENDATIONS FOR DISSEMINATED GONOCOCCAL INFECTION (2001)

Hospitalization is recommended for initial therapy of patients with DGI, particularly those who are unreliable, have uncertain diagnoses, or have purulent synovial effusions, endocarditis, or meningitis (70). Whether pregnant patients with DGI should be hospitalized for bed rest and close observation for the occurrence of preterm labor or intrauterine infection has not been established. Until further information is available, our policy has been to treat pregnant women on an inpatient basis.

Meningitis and endocarditis caused by *N. gonorrhoeae* require high-dose intravenous treatment with ceftriaxone (1 to 2 g intravenously every 12 hours). Gonococcal meningitis should be treated for 10 to 14 days and endocarditis for 4

weeks. Treatment of complicated DGI should be undertaken in consultation with an expert (70).

Pharyngeal Gonorrhea

The recommended regimens for pharyngeal gonorrhea include ceftriaxone (250 mg intramuscularly as a single dose), ciprofloxacin (500 mg orally in a single dose), or ofloxacin (400 mg orally in a single dose) (70). Although chlamydial coinfection of the pharynx is rare, coinfection at genital sites may occur. Thus, concomitant treatment for chlamydia with azithromycin (1 g orally in a single dose) or doxycycline (100 mg orally twice a day for 7 days) is recommended. Gonococcal infection of the pharynx is more difficult to eradicate than that at anogenital sites. Such patients should have repeated cultures at 4 to 7 days after treatment to document cure.

Gonococcal Pelvic Inflammatory Disease

Approximately 25% to 50% of patients with PID have gonococci isolated from their cervix. Treatment of PID is discussed in detail in Chapter 14 (Pelvic Inflammatory Disease).

Gonococcal Ophthalmia

Gonococcal ophthalmia is usually an infection of the neonate. However, the gonococcus can cause adult conjunctivitis. Because untreated gonococcal ophthalmia is highly contagious, the CDC recommends that neonates with gonococcal ophthalmia be hospitalized and isolated for 24 hours after initiation of therapy (70). Ceftriaxone (25 to 50 mg per kilogram of body weight per day intravenously or intramuscularly in a single dose, not to exceed 125 mg) is the therapy of choice. Eyes should be irrigated immediately with saline or buffered ophthalmic solutions and then irrigated at hourly intervals until the discharge is eliminated. Topical antibiotic preparations alone are neither sufficient nor required when appropriate systemic antibiotic therapy is given. Infants with gonococcal ophthalmia should be evaluated for signs of disseminated infection (e.g., sepsis, arthritis, and meningitis) (70). Many pediatricians continue antibiotic therapy until culture results are negative at 48 to 72 hours. Adults with gonococcal conjunctivitis should receive treatment with ceftriaxone (1 g intramuscularly as a single dose).

Prevention

The increasing frequency of asymptomatic gonorrheal infection in women makes screening for *N. gonorrhoeae* during the antepartum period an important aspect of prevention of the perinatal morbidity associated with this organism. Additionally, the use of silver nitrate (1%) aqueous solution or ophthalmic ointments containing tetracycline (1%) or erythromycin (0.5%) should be instilled into the conjunctiva of all newborns to protect against gonococcal conjunctivitis. Single-use tubes or ampules are preferable to multiuse tubes. The CDC recommends that infants born to mothers who have untreated gonorrhea are at high risk for infection and should receive prophylactic treatment with ceftriaxone (25 to 50 mg intravenously or intramuscularly, not to exceed 125 mg in a single dose) (70).

Most important to any prevention effort is the treatment of sexual contacts. Even

those without symptoms must be treated if the cycle of infection is to be halted. Hopefully, the efforts to develop gonococcal vaccines will bear fruit. Of particular interest are the attempts to develop vaccines for the prevention of gonococcal PID and its associated legacy of infertility and ectopic pregnancies.

SYPHILIS

Syphilis is a chronic systemic infectious process due to the spirochete *Treponema palladium* subspecies *Pallidum.* In the late 1980s, syphilis again emerged in epidemic form in the United States, with significant increases in the incidence of primary and secondary syphilis and particularly increases in the incidence of syphilis in pregnancy and congenital syphilis (1,2). Fortunately, since 1991, syphilis rates in the United States have sharply declined (3,4).

It has been recognized for several centuries that primary, secondary, or early latent syphilis in pregnant women caused infection of the fetus, with resultant stillbirths, premature births, congenital abnormalities, and active disease at birth. Because of this significant morbidity, great emphasis has been placed on routine screening of all pregnant women for the presence of syphilis. Acquisition, with the exception of congenital syphilis, is generally through sexual contact. *T. palladium* is capable of entering the body through apparent breaks in mucosal surfaces or abraded areas of the skin. Subsequently, the chancre (the primary lesion) appears at the site of entry of the spirochetes. The chancre, if untreated, resolves within 3 to 6 weeks and is followed by a secondary stage. Secondary syphilis is a systemic disease with dermatologic manifestations, lymphadenopathy, and spirochetemia, which lasts 2 to 6 weeks. This stage is also self-limiting, and with resolution of the secondary stage, the patient enters the latent phase, in which there are no clinical manifestations of disease. Individuals with primary, secondary, or early latent (up to 1 year) syphilis have replicating treponemal organisms and are capable of transmitting syphilis to susceptible hosts. Without therapy, approximately one third of patients develop tertiary syphilis with progressive damage to the central nervous system (CNS), cardiovascular system, musculoskeletal system, or other parenchyma.

T. palladium subspecies *Pallidum* is the etiologic agent of venereal syphilis. It is a strict anaerobic spirochete and obligate human parasite. The organism has never been grown *in vitro* in the laboratory. However, it can be grown in laboratory animals, particularly rabbits. Because no *in vitro* system for culture of *T. palladium* is available, diagnostic efforts must rely on direct smears or serologic tests. Other treponemal species of public health importance include *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (endemic syphilis), and *T. carateum* (pinto) (5).

Epidemiology

In the United States, the incidence of primary and secondary syphilis (best indicator of incidence trends) rose during World War II, reaching a peak in 1947 of 76 cases per 100,000 population (6). After the introduction of penicillin into clinical practice, the incidence of primary and secondary syphilis fell dramatically, reaching a nadir of 4 cases per 100,000 by the late 1950s (Fig. 7.2). Beginning in 1959, this trend reversed, with a rapid rise in incidence among men and women that reached a level of 12 per 100,000 by 1965 (a threefold increase). As noted by Aral and Holmes (6),

this resurgence was due to several factors including decreased governmental expenditures at federal, state, and local levels for STD control; deemphasis on syphilis in medical teaching; and a shift in clinical management of syphilis from public health clinics to the private sector as penicillin became available. From 1965 through 1982, there was steady but slow increase in the incidence of reported cases of primary and secondary syphilis, which peaked in 1982 at 14.6 cases per 100,000 persons. Much of this increase was due to increased rates among homosexual and bisexual men (7). From 1982 until 1985, there was a 22% decrease in reported cases of primary and secondary syphilis. In large part, this decrease occurred among White homosexual and bisexual men (1,2) probably due to changes in sexual behavior as a result of the AIDS epidemic.

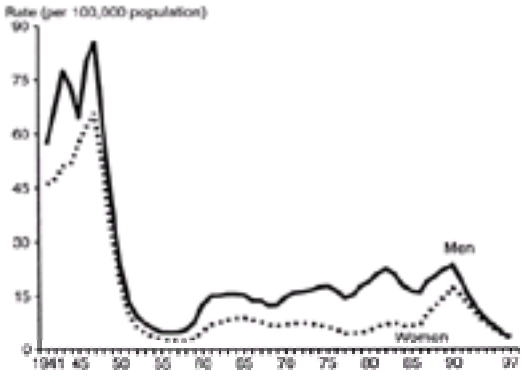


FIGURE 7.2. Trends in incidence of reported primary and secondary syphilis by gender, United States, 1941–1997. (From Aral SO, Holmes KK. Social and behavioral determinants of the epidemiology of STDs: industrialized and developing countries. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually transmitted diseases.* New York: McGraw-Hill, 1999:39–76, with permission.)

Commencing in 1985, the United States experienced the most recent epidemic of syphilis (3,8,9 and 10). From 1985 to 1990, the incidence of primary and secondary syphilis rose sharply, reaching a peak in 1990 of 23.5 cases and 17.3 cases per 100,000 in men and women, respectively (3,6,8,9). Much of the increase occurred among African American men and women. This increased spread of syphilis has been linked to increased use of illicit drugs, particularly “crack cocaine,” and high-risk sexual behavior associated with drug abuse (11,12 and 13). In 1991, the rates of primary and secondary syphilis began to fall dramatically, declining to a level of 2.6 cases per 100,000 for 1998 (Fig. 7.3) (4). During 1998, the highest rates of syphilis continued to be reported in the South and among African Americans, with 17.2 cases per 100,000 compared with 2.8 per 100,000 for Native Americans, 1.5 per 100,000 for Hispanics, 0.5 per 100,000 for Whites, and 0.4 per 100,000 for Asians/Pacific Islanders (4). Between 1991 and 1998, the reported cases of primary and secondary syphilis decreased from 43,500 to 6,993 cases (4,9,10). The 6,993 cases and rate (2.6 per 100,000) of primary and secondary syphilis reported in the United States in 1998 are record lows, representing a 19% decrease in cases from 1997 and an 86% decrease from the 50,578 cases reported in 1990 (rate, 20.3 per 100,000), the peak of the most recent U.S. epidemic (4). It is estimated that three unreported cases exist

for every reported case. Therefore, about 120,000 total cases of syphilis and 20,000 cases of primary and secondary syphilis occur annually in the United States. Chesson et al. (14) have estimated that the annual direct and indirect cost of syphilis is $966 million.

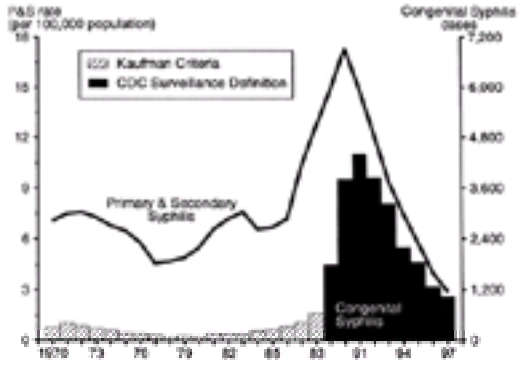


FIGURE 7.3. Rates of primary and secondary syphilis by year, United States, 1970–1998. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1998. *MMWR Morb Mortal Wkly Rep* 1999;48:873.)

As reported by the CDC, trends in congenital syphilis rates follow by approximately 1 year the rates of primary and secondary syphilis (15). Thus, concomitant with the last epidemic of syphilis in the late 1980s and early 1990s, an epidemic of congenital syphilis occurred from 1986 to 1992. Whereas less than 350 cases of congenital syphilis were reported in 1986, there were 3,850 cases of congenital syphilis reported in 1992, with an incidence rate of nearly 100 per 100,000 livebirths (3,15,16). Most cases occurred in New York, California, Florida, Texas, and Michigan (1). Nearly 90% of congenital syphilis patients were Black or Hispanic, and one half were born to mothers who did not receive any prenatal care (1). To some extent, the new case definition for congenital syphilis proposed by the CDC in 1991 contributed in part to the increase in reported cases (17).

Mirroring the decrease in the primary and secondary syphilis rate since 1991, the rate of congenital syphilis began to decline in 1992 (3,18). From 1992 to 1998, the congenital syphilis rate declined 78.2% (Fig. 7.4). Thus, in 1998, 801 cases of congenital syphilis were reported, for a rate of 20.6 per 100,000 livebirths (3). The rates remained disproportionately high in the southeastern United States and among minority racial ethnic populations (3). The CDC reported that more than 80% of reported cases of congenital syphilis occurred because mothers received either no penicillin treatment or inadequate treatment, and no prenatal care occurred in 35.8% of the cases (3).

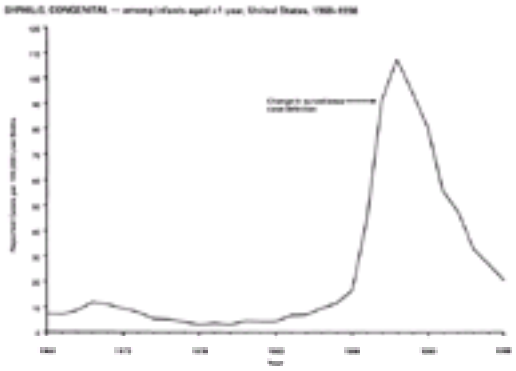


FIGURE 7.4. Congenital syphilis: reported cases in infants younger than 1 year, and rate of primary and secondary syphilis among women in the United States, 1970–1992. (From *MMWR Morb Mortal Wkly Rep* 1993;41:56.)

The previously described trends for syphilis in the United States are very different from those that have been seen in other industrialized nations, where after peaking in the early 1980s, they continuously declined. As a result, syphilis rates in the United States are three to four times greater than those seen in western Europe and Canada (6). On the other hand, eastern European countries, particularly former states in the Soviet Union have been the site of large syphilis epidemics. Aral and Holmes (6) reported that in the Russian Federation, there has been a 50-fold increase in syphilis cases, from 7,991 in 1990 to 392,616 in 1997.

Although syphilis has an epidemiologic pattern similar to that of other STDs, Tramont (19) has noted that syphilis differs from most other STDs in several aspects including (a) syphilis always includes spirochetemia and dissemination throughout the entire body; (b) the disease becomes chronic in one third of untreated or inadequately treated persons, resulting in manifestations affecting any organ; (c) it can affect the fetus *in utero* or intrapartum during passage through the birth canal; and (d) during early phases (the first 4 years) can be nonsexually transmitted by blood transfusion or nonsexual body contact.

Clinical Manifestations

The probability of acquiring syphilis from an infectious partner during a sexual encounter is approximately 50%. After exposure to syphilis, there is an incubation period that ranges from 10 to 90 days before the primary lesion, the chancre, appears (Fig. 7.5). The chancre arises at the spirochete point of entry and is a painless, ulcerated lesion with a raised border and an indurated base. Most commonly, the “hard” chancre of syphilis appears in the genital area. In men, the lesion is easily apparent, and syphilis is often diagnosed in its primary stage in men. Although chancres on the female external genitalia are easily recognized, more commonly, the lesion is on the cervix or in the vagina and not recognized. Thus, the chancre often escapes detection in women, and it is unusual to diagnose the primary stage of syphilis in women. Extragenital sites for chancres include the anus, mouth, oropharynx, and nipple. Usually only a single chancre is present, but multiple chancres occur in up to 30% of cases (19). Although the chancre of syphilis has

many typical characteristics, the appearance of syphilitic lesions is often atypical, and clinicians should have a high index of suspicion for syphilis with all genital ulcerative lesions. Painless inguinal lymphadenopathy is frequently present. The primary chancre, even without treatment, heals spontaneously in 3 to 6 weeks.

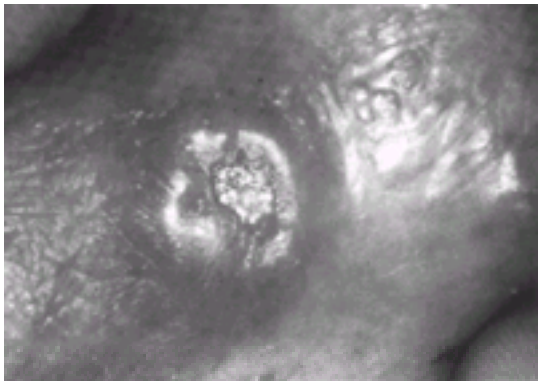


FIGURE 7.5. Primary chancre of syphilis with smooth, raised border and “clean,” nonnecrotic base.

After resolution of the primary stage, the patient enters the secondary or spirochetemia (bacteremia) stage of syphilis. It is critical to recognize that syphilis always disseminates (Fig. 7.6) (19). Thus, any organ can potentially be infected particularly the CNS. In immunologically intact patients, persistent chronic infection seldom occurs, but in persons with dysfunctional immune systems (HIV-infected patients), aggressive or persistent chronic infections are more common (19,20 and 21).

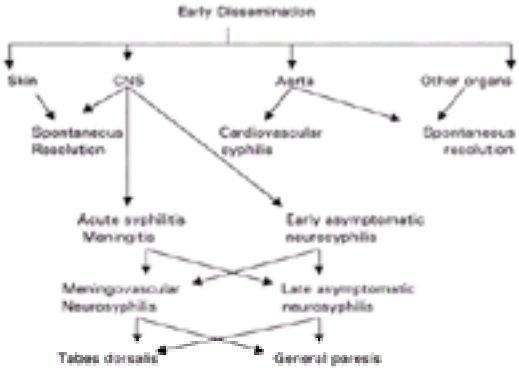


FIGURE 7.6. Pathogenesis of syphilis. (From Tramont EC. Syphilis in adults: from Christopher Columbus to Sir Alexander Fleming to AIDS. *Clin infect Dis* 1995;21:1361–1371.)

T. pallidum is a slow-growing bacterium that divides every 30 to 33 hours and thus requires from 2 to 24 weeks (usually 4 to 10 weeks) after primary inoculation to develop an antigen load that is sufficient to stimulate the immune response responsible for the clinical findings seen in secondary syphilis. Although the secondary stage of syphilis is characterized by involvement of all major organ systems by *T. palladium* (Table 7.13), the secondary stage presents most commonly with skin and mucous membrane lesions. These clinical manifestations of secondary syphilis include a generalized maculopapular rash, which usually begins in the trunk and proximal extremities and spreads to the entire body, particularly involving the palms and soles, mucous patches, condyloma latum, and generalized lymphadenopathy. Chapel (22) has summarized the clinical findings in 105 cases of secondary syphilis. The maculopapular lesions were most common (70%), with the palms and soles being the most common site (50%). Mucosal lesions were noted in 21%, and generalized lymphadenopathy was seen in 85% with a predilection for involvement of epitrochlear nodes. Surprisingly, Chapel (22) reported that more than 40% of these cases had a history of pruritus.

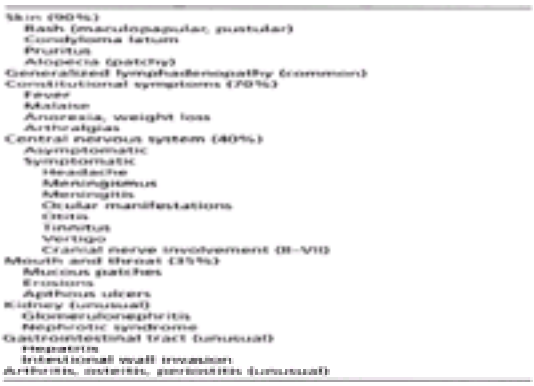


TABLE 7.13. CLINICAL MANIFESTATIONS OF SECONDARY SYPHILIS

During the secondary stage of syphilis, the CNS is invaded by spirochetes in 40% of cases (23,24). Although abnormal levels of protein and cell counts in the cerebrospinal fluid (CSF) are common, and headache or meningismus may develop, frank “aseptic” meningitis is uncommon (1% to 2% of cases) (19). Temporary alopecia, which is patchy, characteristically affects the eyebrows and beard. Even without treatment, these findings of secondary syphilis spontaneously clear within 2 to 6 weeks, and the latent stage of syphilis is entered, in which there is no apparent clinical disease. In the prepenicillin era, about 25% of such patients had a recrudescence of secondary syphilis. These relapses usually occurred within 1 year, and thus the term “early latency” applies to this time period (less than 1 year). The mucocutaneous lesions associated with such relapses are highly contagious. The late latent stage (more than 1 year) is not infectious by sexual transmission, but the spirochete may still be transplacentally transmitted to the fetus.

If treatment is not provided, one third of patients progress and develop tertiary syphilis with involvement of the cardiovascular, central nervous, or musculoskeletal

system, as well as involvement of various organ systems with gummata (late benign tertiary syphilis) (25,26,27 and 28). When tertiary syphilis occurs, one-half of patients develop late benign syphilis (gummata); one fourth, cardiovascular disease; and one fourth, neurologic disease. The cardiovascular manifestations of tertiary syphilis include aortic aneurysm and aortic insufficiency. In the CNS, tertiary disease produces general paresis, tabes dorsalis, optic atrophy, meningovascular syphilis; the Argyll Robertson pupil (does not react to light, but accommodates) is virtually pathognomonic of tertiary syphilis. The pathogenesis of tertiary syphilis is based on the tropism of *T. pallidum* for arterioles, resulting in obliterative endarteritis with subsequent tissue destruction (19).

Although tertiary syphilis has been associated with involvement of the CNS after several years of disease, recent investigations have reported that serious sequelae involving the CNS occur much earlier, particularly in immunocompromised patients (e.g., the HIV-infected patient) (29).

CONGENITAL SYPHILIS

As a direct result of the dramatic increase in the prevalence of syphilis in the late 1980s and early 1990s in the United States, there was also a rapid increase in cases of congenital syphilis. To a large extent, this rise occurred in women in the reproductive age-group; thus, clinicians providing health care to young women, including pregnant women, again became cognizant of the importance of screening for, diagnosing, and treating syphilis early in pregnancy to prevent the ravages of congenital syphilis. After a peak in 1991 of nearly 4,500 cases of congenital syphilis, in 1998, a decrease to 801 cases was reported by the CDC (3).

In the past, syphilis was felt to invade the fetus via transplacental infection only after 16 weeks of gestation, because it was believed that spirochetes were unable to penetrate the Langerhans layer of the placenta. However, it has been documented that *T. palladium* can be transferred across the placenta and infect the fetus earlier. Harter and Benirschke (30) detected spirochetes in fetal tissue from spontaneous abortions at 9 to 10 weeks of gestation. More recently, spirochetes have been demonstrated in amniotic fluid as early as 14 weeks of gestation (31). Clinical manifestations are not apparent until after 16 weeks of gestation when the fetus develops immunocompetence. Thus, the risk to the fetus is present throughout pregnancy. Transmission can also occur during labor and delivery via contact with active genital lesions in the mother (32). The degree of risk to the fetus or neonate is related to the quantity of spirochetes in the maternal bloodstream and correlates with the maternal stage of syphilis (33,34). Pregnancy does not have an effect on the clinical course of syphilis (32). However, pregnancy may confuse or delay the diagnosis of syphilis due to false-positive nontreponemal screening serologic tests, which may occur in pregnancy. On the other hand, syphilis adversely effects pregnancy and untreated syphilis may cause spontaneous abortion, stillbirth, nonimmune hydrops, preterm delivery, and perinatal death (33,34,35,36,37,38,39,40,41,42 and 43). Women with primary or secondary syphilis are more likely to transmit infection to their offspring than those with latent disease. Fiumara et al. (34) reported that during untreated primary or secondary syphilis, virtually 100% of fetuses will be infected, and that there was a 50% probability of congenital syphilis, and half the infants were stillborn, neonatal deaths, or premature; there were almost no healthy full-term infants among mothers with untreated primary or secondary syphilis (Table 7.14). With early latent syphilis, a 40% risk for

congenital syphilis was present: 20% premature, 16% stillbirth, and 4% neonatal death. This risk decreased to 10% in mothers with late syphilis, and in this group, there was no increase in premature or perinatal deaths. Similarly, Ingraham (35) reported that in pregnant women with untreated syphilis of less than 4 years' duration, 41% of liveborn infants had congenital syphilis, versus 2% with disease of more than 4 years' duration. In addition, 25% were stillbirths and 14% died in the neonatal period (35). More recent studies of syphilis in pregnancy during the most recent epidemic of congenital syphilis have confirmed the devastating effect untreated or inadequately treated syphilis has on the fetus and neonate (36,37). Ricci et al. (36) reported their experience with congenital syphilis at the University of Miami/Jackson Memorial Medical Center from 1986 to 1988. During that period, they identified 56 cases of congenital syphilis, which yielded an overall rate of 18.4 cases per 10,000 births, a threefold increase over that time. Mothers of infants with congenital syphilis were predominantly African Americans who lacked prenatal care (67%) and were substance abusers (71%). Nineteen (34%) of the infants with congenital syphilis were stillborn. The mean gestational age (32.3 weeks) and mean birthweight (1,861 g) of liveborn infants with congenital syphilis were significantly lower than those of matched controls. Preterm labor occurred in 85%, and PROM occurred in 36% of congenital syphilis cases. In addition, 21% of congenital syphilis cases showed intrauterine growth retardation.

	Congenital Infection	Perinatal Mortality	Preterm Delivery
Fiumara et al. (34)[a]			
Primary, secondary	50%	50%	
Early latent	40%	20%	20%
Late latent	10%	11%	9%
Ricci et al. (36)[b]	100%	46.4%	85%
MacFarlin et al. (37)[c]	38%	8%	28%

[a]Mothers undiagnosed and untreated during pregnancy.
[b]Evaluated documented cases of congenital syphilis.
[c]Mothers treated with Centers for Disease Control and Prevention recommended regimens.

TABLE 7.14. IMPACT OF SYPHILIS ON PERINATAL OUTCOME

McFarlin et al. (37) reviewed 253 cases of maternal syphilis prospectively identified over a 1-year period at the Hutzel Hospital in Detroit. Using the new CDC surveillance case definition, they identified 72 infants who met the criteria for congenital syphilis. Pregnant women with syphilis were predominantly African American, single, on Medicaid, and multiparous. Among the entire group infected with syphilis, there was a 50.3% incidence of drug abuse, with a 35.8% incidence of cocaine use. Preterm delivery occurred in 28% of mothers infected with syphilis, even if adequately treated for syphilis during pregnancy. There were 10 (13.9%) stillbirths among the 72 cases of congenital syphilis, compared with none among infants without congenital syphilis delivered to mothers with syphilis during pregnancy. Interestingly, 8 (75%) of the 12 women who did not receive antibiotic therapy for syphilis in the congenital syphilis group delivered stillborn infants. Cunningham and Hollier (42) reported that during the recent syphilis epidemic in

Dallas, Texas, from 1988 to 1995, syphilis accounted for 6% of all the stillbirths at Parkland Memorial Hospital. Stillbirth rates due to syphilis have ranged from 5% to 42% in reports from Africa (40).

Coles et al. (43) reviewed 322 cases of congenital syphilis in the years 1989 to 1992 from a congenital syphilis surveillance program in upstate New York. There were 31 (10%) stillbirths and 59 (18%) newborns with clinical evidence of congenital syphilis. The mothers of infants with congenital syphilis were predominantly racial minorities, unmarried, and younger than 30 years (43). Although 89% of the mothers had an identified risk factor for syphilis (e.g., drug abuse, residency in a high syphilis morbidity area, and prior history of syphilis), nearly half of the mothers did not receive prenatal care. Other factors contributing to congenital syphilis were infection late in the pregnancy, treatment less than 30 days before delivery, misdiagnosis or inappropriate treatment of the mother, and no serologic testing during pregnancy (43).

The clinical spectrum in congenital syphilis includes stillbirths, neonatal death, clinical apparent congenital syphilis during the early months of life (early congenital syphilis), and development of the classic stigmata of late congenital syphilis (33,34). Although the most severe effects on pregnancy outcome occur with primary or secondary syphilis, pregnant women diagnosed as having syphilis are usually asymptomatic in the latent stage and have had the disease for more than 1 year. Consequently, most infants (approximately two thirds) with early congenital syphilis are asymptomatic at birth and do not develop evidence of active disease for 3 to 8 weeks. Chancres do not occur unless the disease is acquired at the time of passage through the birth canal. The characteristic manifestations of early congenital syphilis (onset at younger than 2 years) (Table 7.15) include a maculopapular rash that may progress to desquamation or vesicular and bullae formation, snuffles (a flulike syndrome associated with a nasal discharge), mucous patches in the oral pharyngeal cavity, hepatosplenomegaly, jaundice, lymphadenopathy, pseudoparalysis (Parrot disease) due to osteochondritis, chorioretinitis, and iritis (33,34). Both cutaneous and mucous lesions contain spirochetes that can be seen on dark-field examination. Bone abnormalities are the only manifestation in approximately 20% of infants with early and congenital syphilis (44). Characteristically, lesions occur in long bones, particularly the humerus and femur, and have a classic radiographic “moth-eaten” appearance (32).

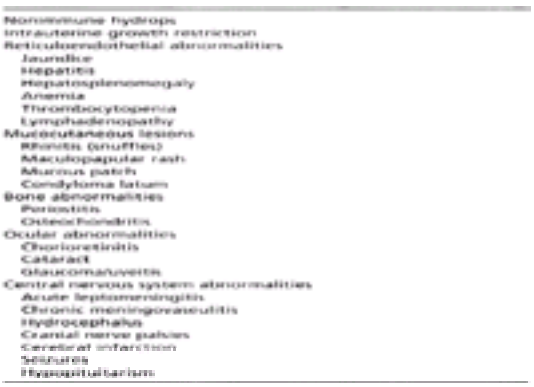


TABLE 7.15. CLINICAL MANIFESTATIONS OF EARLY CONGENITAL SYPHILIS

Untreated or incompletely treated early congenital syphilis will progress to the classic manifestations of late congenital syphilis (Table 7.16). These include Hutchinson teeth, mulberry molars, interstitial keratitis, eighth nerve deafness, saddle nose, rhagades, saber shins, and neurologic manifestations (mental retardation, hydrocephalus, general paresis, optic nerve atrophy, and Clutton joints). Hutchinson triad, consisting of Hutchinson teeth, interstitial keratitis, and eighth nerve deafness, is pathognomonic for congenital syphilis. These stigmata associated with late congenital syphilis are the result of scarring induced by early lesions or reactions to persistent inflammation (33).

Neurologic abnormalities
Mental retardation
Eighth nerve deafness
Hydrocephalus
Dental abnormalities
Peg-shaped upper incisors (Hutchison teeth)
Mulberry molars
Perioral fissures (rhagades)
Skeletal abnormalities
Frontal bossing
Short mandible
Saddle nose
Protruding mandible
High-arched palate
Saber shins
Flaring scapulae
Bilateral knee effusions

TABLE 7.16. MANIFESTATIONS OF LATE CONGENITAL SYPHILIS

Diagnosis

The most specific and sensitive method for diagnosing syphilis is demonstration of *T. palladium* in fresh specimens obtained from the lesions of infected individuals. Dark-field examination and direct fluorescent antibody tests are the definitive methods for diagnosing early syphilis. This methodology is only applicable to the lesions of primary or secondary syphilis. A specimen for dark-field examination or fluorescent antibody test should be obtained from any lesion suspected of being a chancre or manifestation of secondary syphilis. To obtain the specimen, the physician cleans the lesion with normal saline, and after it is dried, it is abraded with cotton gauze until minimal bleeding is initiated. Then with pressure applied to the lesion, clear serum is expressed, which is applied to a slide. A coverslip is placed over the serum and sealed at its periphery with petroleum jelly. Specimens for dark-field examination should be evaluated promptly. Collection of specimens for direct fluorescent antibody tests is similar to that for dark-field examination. However, slides are air dried and heat fixed or air dried and fixed with acetone or 10% methanol. Then staining is performed. The direct fluorescent antibody test can be performed on paraffin-embedded biopsy or autopsy material (45).

However, most men and nearly all women who are diagnosed as having syphilis are usually asymptomatic and in the latent stage, so the diagnosis is most often based

on serologic testing results. The serologic tests are classified into two types: nonspecific tests for reagin-type antibodies and specific antitreponemal antibody tests (46,47). Nonspecific antibody tests for syphilis available today include the Veneral Disease Research Laboratories (VDRL) and the rapid plasma reagin (RPR) test. These are used as screening tests. All pregnant women should be screened at their initial prenatal visit with one of these nontreponemal tests. High-risk patients should be rescreened at 32 to 34 weeks of gestation. The titer levels of nontreponemal tests usually correlate with active disease; thus, results of the VDRL or RPR test should be quantitated (47). A fourfold change in titer level is required to document a significant change. Sequential serologic testing should be performed using the same testing method, preferably by the same laboratory (47). Treponema-specific tests are employed for confirming the diagnosis of syphilis in patients that have reactive VDRL or RPR tests. These tests include the *T. pallidum* immobilization (TPI) test, the fluorescent treponemal antibody absorbed (FTA-ABS), and the microhemagglutination–*T. pallidum* (MHA-TP) test. The MHA-TP test is less expensive and easier to perform; thus, it has largely replaced the FTA-ABS test for confirmation of positive screening test results. In most patients, the nontreponemal test will eventually become nonreactive after treatment (47). However, nontreponemal antibodies persist at a low titer level for a long time, occasionally for the remainder of life in some patients. On the other hand, most patients with reactive treponemal test results will have reactive test results for the remainder of their lives, regardless of treatment or disease activity (47). The CDC suggests that in 15% to 25% of patients treated during the primary stage of syphilis, treponemal test results will revert to negative after 2 to 3 years (44).

When the syphilitic chancre first appears, both the nonspecific antibody test results (VDRL and RPR) and the treponema-specific test results (FTA-ABS and MHA-TP) may be nonreactive. Therefore, lesions of syphilitic chancres should be sampled for a dark-field examination. The presence of spirochetes on this examination is the *sine qua non* for the diagnosis of primary syphilis. During the several weeks after the chancre appears, these serum test results become positive; by 4 to 6 weeks, 100% of patients with primary syphilis have positive nonspecific and specific treponemal serum test results. Both nontreponemal and treponemal serum test results will be positive during the secondary and latent stages of syphilis.

The CDC recommends that all pregnant women should be screened serologically for syphilis early in pregnancy (i.e., at the first prenatal visit) (47). For populations in which the use of prenatal care is not optimal, the CDC recommends that RPR card test screening (a rapid screening test for syphilis) be performed at the time pregnancy is diagnosed and treatment should be given if the card test result is positive (47). In populations with a high prevalence of syphilis or for high-risk patients, serologic testing should be performed twice during the third trimester at 28 weeks of gestation and at delivery (47). The CDC also suggests that any women delivering a stillborn after 20 weeks of gestation be screened for syphilis. Further, it is recommended that no infant should be discharged from the hospital without the maternal serologic status having been determined at least once in pregnancy (47). Pregnant women with a reactive nontreponemal test result should promptly have a quantitative nontreponemal test (RPR or VDRL), and a confirmatory treponemal test such as the MHA-TP or FTA-ABS should be performed. False-positive reactions can occur with all of these tests but are uncommon with the specific antitreponemal tests. Common causes of false-positive nontreponemal test results include viral infections, autoimmune diseases (systemic lupus, sarcoidosis, and rheumatoid arthritis), narcotics abuse, and pregnancy. The false-positive test results with nontreponemal

tests are most often only weak or borderline reactions. In pregnancy, it is best to consider seropositive women infected, unless an adequate treatment history is documented in the medical record and sequential serologic antibody titer levels have declined (47).

Although false-positive results with nontreponemal serologic tests have been demonstrated in many conditions including pregnancy, they can be identified by using treponemal serologic tests, dark-field examination, or serial screening. On the other hand, a false-negative result leads to failure to be treated, which in pregnancy can lead to devastating results. The prozone phenomenon, which occurs when an excess of antibody in the sera prevents formation of the antigen-antibody complex needed to visualize a positive reaction, can cause a false-negative result with the VDRL or PRP test. It occurs in approximately 2% of cases of primary or secondary syphilis (48). Serum dilution reestablishes the appropriate concentration of antibody and corrects the situation. The prozone phenomenon is of concern, particularly in asymptomatic pregnant women. Thus, it is recommended that serum dilution be performed for any pregnant women at high risk for syphilis (49).

For most HIV-infected patients, the serologic tests for syphilis appear to be accurate and reliable for both diagnosis of syphilis and evaluation of treatment response (47). Occasionally, HIV-infected patients have abnormal serologic test results, with unusually high or low titer levels or fluctuating titer levels. In such patients who have clinical findings suggestive of early syphilis, the CDC suggests using biopsy and direct microscopy (47).

Controversy has arisen over whether all patients (including pregnant women) who are asymptomatic but have a positive serologic diagnosis of syphilis should have a spinal tap for the detection of asymptomatic neurosyphilis. The spinal tap ensures proper treatment of neurosyphilis (see the later section on treatment). Evaluation of patients with syphilis with neurologic abnormalities must include CSF examination (47). Although there is a high frequency of CSF abnormalities (elevated cell count, elevated protein concentration, reactive VDRL test results), in early syphilis, treatment results are good; thus, CSF examination is not necessary in asymptomatic early syphilis (47). The CDC recommends that all patients with latent syphilis be evaluated clinically for evidence of tertiary disease (e.g., aortitis, neurosyphilis, gumma, or iritis). Patients who demonstrate any of the criteria listed in Table 7.17 should have a prompt CSF examination (47). With syphilis of more than 1 year's duration, CSF examination should be considered. CSF demonstrating pleocytosis, elevated protein concentrations, and a reactive VDRL test result is diagnostic of active neurosyphilis. Several studies have suggested that the VDRL test is relatively insensitive for the detection of neurosyphilis and recommend that the FTA-ABS or the *T. pallidum* hemagglutination test be done on CSF specimens (50,51).

Neurologic or opthalmic signs or symptoms
Evidence of active tertiary syphilis (e.g., aortitis, gumma, and iritis)
Treatment failure
Human immunodeficiency virus infection with late latent syphilis or syphilis of unknown duration

TABLE 7.17. CRITERIA FOR PERFORMANCE OF CEREBROSPINAL FLUID EXAMINATION IN PATIENTS WITH LATENT SYPHILIS TO EXCLUDE NEUROSYPHILIS

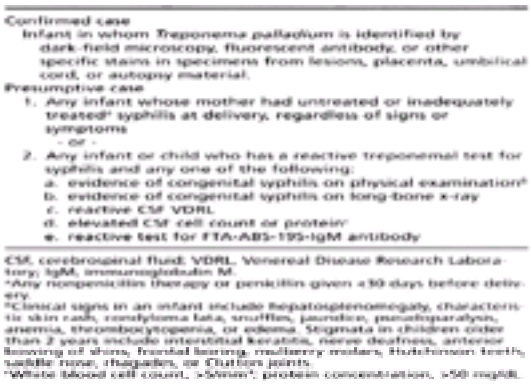
The CDC emphasizes that no single test can be used to diagnose neurosyphilis (47). The diagnosis can be made using various combinations of reactive serologic tests, abnormal CSF cell count, elevated protein level, or a reactive CSF VDRL test result. The RPR test should not be performed on CSF. When reactive in a nonbloody tap, a CSF VDRL test result is diagnostic of neurosyphilis. However, it may be nonreactive in the presence of neurosyphilis. When active neurosyphilis is present, the CSF leukocyte count is usually more than five white blood cells (WBCs) per cubic millimeter. The CSF WBC level is also a sensitive measure of response to treatment (47).

The diagnosis of reinfection or persistence of active syphilis can be made in patients previously known to have syphilis by following the titer level of the quantitative VDRL test. With successful therapy, the VDRL titer level should decrease and become negligible within 6 to 12 months in early syphilis and 12 to 18 months with late syphilis of more than 1 year's duration. A rising titer level indicates a need for further diagnostic measures such as a spinal tap and appropriate treatment.

Congenital syphilis is easily diagnosed in the clinically apparent case in which a jaundiced, hydropic baby with florid disease and a large edematous placenta is delivered and laboratory studies confirm the presence of the disease, particularly demonstration of *T. pallidum* by dark-field examination. However, most infected newborns are asymptomatic at birth but have a positive nonspecific test result for syphilis in the cord blood. In this group, the diagnosis must be based entirely on serology. The problem is attempting to determine whether the cord blood serology is merely immunoglobulin G (IgG) antibody passively transferred from the mother or whether it is IgM antibody indicative of a fetal infection. The FTA-ABS also is an IgG antibody and crosses the placenta. An FTA-ABS-19S-IgM test has been developed; however, only specialized laboratories can perform this test. In addition, a recently treated mother may cause diagnostic difficulty in the neonate. If an infant's seropositivity is due to passive transfer of maternal IgG antibodies, a progressive decrease in the VDRL titer occurs, and the titer becomes negative within 3 months of delivery. Any infant with a reactive VDRL test result but no clinical evidence of syphilis should be followed with serial monthly quantitative VDRL tests for at least 9

months. A rising titer level indicates active disease and the need for therapy. Infected infants may be asymptomatic and the serum VDRL test results may be normal if maternal infection occurred late in pregnancy. Most clinicians accept a positive VDRL test result confirmed by the FTA-ABS or MHA-TP test on cord blood as proof of syphilis until proven otherwise and would treat the neonate immediately rather than perform serial observations. The CDC suggests that a specimen from the neonate is preferred because of possible maternal contamination of cord blood. Because the transplacental passage of antibodies makes interpretation of reactive serologic tests in newborns difficult, treatment decisions are often based on (a) confirmation of syphilis in mother, (b) adequacy of maternal treatment, (c) presence of clinical, laboratory, or radiographic evidence of syphilis in the infant, and (d) comparison of the infant's nontreponemal serologic test titer level with that of the mother (44).

In the past, a complicated definition for congenital syphilis was used clinically. This clinical case definition involved physical examination, laboratory, and radiographic results and follow-up serologic data (52). Recently, the CDC implemented a new case definition for congenital syphilis surveillance (17,53). The new congenital syphilis case definition is provided in Table 7.18. With the current definition, not only infants with clinical evidence of active syphilis, but also asymptomatic infants and stillbirths born to mothers with untreated or inadequately treated syphilis are included. A diagnosis of congenital syphilis can be confirmed by identifying spirochetes in suspicious lesions, body fluids, or tissues with dark-field microscopy, silver staining, immunofluorescence, or PCR for *T. pallidum* DNA (54). The placenta should be sent for histologic examination when congenital syphilis is suspected. A triad of enlarged hypercellular villi, proliferative fetal vasculature changes, and acute or chronic villitis is often present (54). The CDC suggests that any infant of a seropositive mother should undergo a thorough examination for evidence of congenital syphilis. This should include serologic testing, a CSF evaluation for cell count, protein and VDRL, and long bone radiographs (47). Immunofluorescent antigen (IFA) testing for *T. pallidum* in tissue from stillbirths associated with maternal syphilis has been shown to be superior to silver staining for identification of treponemes (55). Thus, all stillbirths associated with positive maternal serology for syphilis should be evaluated for congenital syphilis with IFA and silver stains (47).



Confirmed case
Infant in whom *Treponema pallidum* is identified by dark-field microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material.

Presumptive case
1. Any infant whose mother had untreated or inadequately treated[a] syphilis at delivery, regardless of signs or symptoms
   - or -
2. Any infant or child who has a reactive treponemal test for syphilis and any one of the following:
   a. evidence of congenital syphilis on physical examination[b]
   b. evidence of congenital syphilis on long-bone x-ray
   c. reactive CSF VDRL
   d. elevated CSF cell count or protein[c]
   e. reactive test for FTA-ABS-19S-IgM antibody

CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory; IgM, immunoglobulin M.
[a]Any nonpenicillin therapy or penicillin given <30 days before delivery.
[b]Clinical signs in an infant include hepatosplenomegaly, characteristic skin rash, condyloma lata, snuffles, jaundice, pseudoparalysis, anemia, thrombocytopenia, or edema. Stigmata in children older than 2 years include interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades, or Clutton joints.
[c]White blood cell count, >5/mm³; protein concentration, >50 mg/dL.

TABLE 7.18. CONGENITAL SYPHILIS CASE DEFINITION: CENTERS FOR DISEASE CONTROL, 1991

Dobson et al. (56) demonstrated that the finding of IgM antibody against the 47- or 37-kd antigens of *T. palladium* was useful in diagnosing congenital syphilis at birth. These authors used the technique of Western blotting to detect the antigens of *T. palladium* recognized by IgM antibodies. Meyer et al. (57) used Western blotting to detect IgM antibodies specific for *T. pallidum* antigens (57). In asymptomatic congenital syphilis, 13 of 14 (92% sensitivity) were positive and 10 of 12 (83% sensitivity) of asymptomatic infants who later developed congenital syphilis were positive.

In utero prenatal diagnosis of congenital infection with syphilis has been reported. Ultrasonography has been the primary technique used. Sonographic findings associated with fetal syphilis include fetal hydrops in the presence of maternal syphilis, hepatosplenomegaly, and placentomegaly (58,59 and 60). Gastrointestinal tract obstruction and dilation have also been identified with ultrasound in fetal syphilis (60,61).

Amniocentesis has been used to demonstrate the presence of *T. pallidum* in the amniotic fluid of fetuses infected with syphilis. Wendel et al. (62) studied five gravidas with untreated syphilis and fetal deaths with sonographic examination and amniocentesis. In all five cases, dark-field microscopy of the amniotic fluid demonstrated spirochetes with morphology and motility characteristic of *T. palladium.* Subsequently, Wendel et al. (63) performed amniocentesis for evaluation of syphilis in two pregnancies with secondary syphilis. Motile spirochetes typical of *T. palladium* were seen with dark-field examination of the amniotic fluid. The presence of *T. palladium* was confirmed by antitreponemal monoclonal antibody immunofluorescence assays and by rabbit infectivity tests (RITs) using amniotic fluid. Nathan et al. (59) detected spirochetes using RITs in association with sonographic evidence of hepatomegaly. Grimprel et al. (64) detected *T. pallidum* in amniotic fluid using PCR demonstrating a sensitivity of 91% and specificity of 100%, compared with RITs (64). Wendel et al. (63) demonstrated that cordocentesis can detect fetal infection with syphilis directly using fetal IgM specific for *T. pallidum* and indirectly by demonstrating anemia, thrombocytopenia, and elevated liver enzyme levels. Nonimmune fetal hydrops associated with maternal infection with syphilis has been recently reported, in which all three infected infants were treated and survived (58). This was in contradistinction to earlier reports in which six (85.7%) of seven hydropic syphilis-infected infants died (65,66). This finding highlights the importance of evaluating fetuses with nonimmune hydrops for the possibility of *in utero* infection, including syphilis, particularly in association with hepatomegaly, placentomegaly, and bowel obstruction.

Treatment

All patients with a history of sexual contact with a person with documented syphilis or either a positive dark-field examination result or serologic evidence of syphilis with a specific treponemal test should be treated. In addition, those in whom the diagnosis cannot be ruled out with certainty or in those with previous treatment who have evidence of reinfection such as dark-field–positive lesions or a fourfold rise in titer level of a quantitative nontreponemal test should receive appropriate treatment.

Parenteral penicillin G is the preferred drug for the treatment of all stages of syphilis

(47). The efficacy of penicillin in treating syphilis has been established through clinical experience for more than 50 years. The type of penicillin preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline) and the dosage and length of treatment are dependent on the stage of syphilis and the clinical manifestations present. Parenteral penicillin G is the only therapy with documented efficacy for treating neurosyphilis or syphilis in pregnancy. Thus, the CDC recommends that patients with neurosyphilis and pregnant women with syphilis who report being allergic to penicillin should be treated with penicillin after desensitization (47). Unfortunately, the minor determinants required for penicillin skin testing are not available commercially, so skin testing is not necessary in all patients.

Table 7.19 contains the CDC-recommended treatment regimens for the various stages of syphilis in nonpregnant, pregnant, and HIV-infected patients. As noted by the CDC, 40 years of experience demonstrate that parenteral penicillin G is effective in achieving local cure (healing of lesions and prevention sexual transmission) and in preventing tertiary syphilis when used for the treatment of primary and secondary syphilis (47). Thus, for patients (nonpregnant and pregnant) not allergic to penicillin, the recommended regimen for primary and secondary syphilis is penicillin G benzathine at 2.4 million units intramuscularly in a single dose. The CDC suggests that all patients with syphilis be tested for HIV infection (47). In areas with high HIV prevalence, patients with primary syphilis should be retested for HIV in 3 months. Patients with syphilis who have symptoms or signs suggestive of neurologic or ophthalmic disease should have CSF analysis and slit-lamp examination to rule out neurosyphilis and syphilitic eye disease, respectively (47). Although invasion of the CSF by *T. palladium* with accompanying CSF abnormalities is common among patients with primary or secondary syphilis, few patients develop neurosyphilis when treated with the recommended course of penicillin G benzathine. Therefore, spinal tap is not recommended for routine evaluation in primary or secondary syphilis but is reserved for those in whom clinical signs or symptoms of neurologic disease are present or for patients who fail to respond to treatment (47).

TABLE 7.19. CENTERS FOR DISEASE CONTROL 2001 RECOMMENDED TREATMENT OF SYPHILIS IN ADULTS

In nonpregnant patients with primary or secondary syphilis who are allergic to penicillin, treatment with doxycycline (100 mg bid for 2 weeks) or tetracycline (500

mg qid for 2 weeks) is suggested. Ceftriaxone may also be considered. Pharmacologic and bacteriologic information indicates that ceftriaxone should be an effective alternative for the treatment of primary and secondary syphilis (47). However, the CDC cautions that data are limited and clinical experience insufficient to determine the risk of late failures (47). Moreover, the optimal dose and duration of treatment have not been determined for ceftriaxone. The CDC suggests that a daily regimen of ceftriaxone at 1 g may be used if treponemicidal levels in blood can be maintained for 8 to 10 days (47).

An additional alternative in nonpregnant patients allergic to penicillin, in whom compliance and follow-up can be ensured, is erythromycin (500 mg orally four times a day for 2 weeks) (47). However, erythromycin is less effective than other recommendations for treatment of primary or secondary syphilis (47). Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see later discussion).

Assessing response to treatment is based on serologic titer levels and clinical findings. With primary or secondary syphilis, patients should be reexamined clinically and serologically at 6 months and 12 months posttreatment (47). HIV-infected patients should be examined more frequently, at 3-month intervals. Quantitative nontreponemal titer levels (VDRL or RPR) should decline fourfold by 6 months after treatment (47). Failure to do so identifies patients at risk for treatment failure and those who should be screened for HIV infection. At a minimum, such patients require additional clinical and serologic follow-up. When follow-up cannot be ensured, re-treatment is recommended. Those patients with persistent or recurring signs or symptoms or who have a fourfold rise in titer level of nontreponemal testing are considered to be failures or to be reinfected (47). These patients also require re-treatment after evaluation for HIV disease. For re-treatment, it is best to provide three weekly injections of penicillin G benzathine at 2.4 million units intramuscularly, unless CSF examination demonstrates the presence of neurosyphilis, which requires treatment as discussed later.

The goal in treatment of latent syphilis is to prevent occurrence of tertiary syphilis (47). Latent syphilis that has been acquired within the preceding year is defined as early latent syphilis. To establish that syphilis was acquired in the preceding year, one of the following should be present: (a) documented seroconversion, (b) unequivocal symptoms of primary or secondary syphilis, or (c) a sex partner who had primary, secondary, or latent syphilis of less than 1 year's duration (47). All other patients are considered to have syphilis of unknown duration and are classified and managed as having late latent syphilis (more than 1 year's duration).

For patients not allergic to penicillin with early latent syphilis and with normal CSF examination results (if performed), the recommended regimen is penicillin G benzathine at 2.4 million units intramuscularly in a single dose. With late latent syphilis (more than 1 year's duration or unknown duration), the recommendation is penicillin G benzathine at 7.2 million units total, administered as three doses of 2.4 million units intramuscularly each, at 1-week intervals. In nonpregnant patients with latent syphilis who are allergic to penicillin, nonpenicillin therapy should be used only after CSF examination rules our neurosyphilis. Either doxycycline (100 mg orally twice a day) or tetracycline (500 mg orally four times a day) is recommended in such individuals. For early latent syphilis, the duration of therapy is 2 weeks and with more than 1 year's duration, it is 4 weeks (47). Pregnant patients allergic to penicillin

should be desensitized (see later discussion) and treated with penicillin.

The CDC recommends that all patients with latent syphilis should be evaluated clinically for evidence of tertiary syphilis. Although the recommended therapy for latent syphilis may not be optimal therapy for asymptomatic neurosyphilis, the yield of diagnosed cases of neurosyphilis from CSF examination is low, so routine spinal tap is not recommended (47). However, patients with the criteria listed in Table 7.17 should have a CSF examination to exclude neurosyphilis before treatment. If CSF examination demonstrates abnormalities suggestive of CNS syphilis, treatment like that for neurosyphilis should be instituted (47).

Follow-up in patients with latent syphilis requires that quantitative nontreponemal serologic tests be repeated at 6 months, 12 months, and 24 months after treatment (47). If titer levels increase fourfold or if an initial titer level of more than 1 : 32 fails to decline fourfold within 12 to 24 months, or if the patient develops signs or symptoms of syphilis, the patient should be evaluated for neurosyphilis and re-treated appropriately depending on the findings of CSF examination.

Patients with late (tertiary) syphilis findings of gumma or cardiovascular disease (not neurosyphilis) should be treated with penicillin G benzathine at 7.2 million units total, administered as three doses of 2.4 million units intramuscularly, at 1-week intervals. Penicillin-allergic nonpregnant patients are treated according to the treatment regimens recommended for those with late latent syphilis (Table 7.19). Pregnant patients allergic to penicillin should be desensitized and treated with penicillin (see later discussion) (47). All patients with symptomatic late syphilis should undergo CSF examination before therapy to exclude neurosyphilis (47).

Disease involving the CNS can occur during any stage of syphilis (47). Thus, any patient with syphilis who demonstrates clinical evidence of neurologic involvement such as ophthalmic symptoms, auditory symptoms, cranial nerve palsies, or symptoms or signs of meningitis should be evaluated with a lumbar puncture. Syphilis uveitis or other syphilitic eye diseases frequently are associated with neurosyphilis and thus should be treated per recommendations for neurosyphilis and undergo CSF testing in follow-up to assess treatment response (47). Patients with neurosyphilis or syphilitic eye disease and who are not allergic to penicillin should be treated with 18 to 24 million units of aqueous crystalline penicillin G daily, administered as 3 to 4 million units intravenously every 4 hours for 10 to 14 days. For patients in whom compliance can be ensured, 2.4 million units of penicillin procaine intramuscularly daily, plus probenecid at 500 mg orally four times a day for 10 to 14 days, is an alternative (47). Because these regimens are shorter than those used for late syphilis without neurosyphilis, some experts administer penicillin G benzathine at 2.4 million units intramuscularly after completion of the neurosyphilis treatment regimen (47).

If CSF pleocytosis was present on the initial lumbar puncture, a CSF examination should be repeated every 6 months until the cell count is within the normal reference range (47). Although follow-up CSF examinations can also assess changes in CSF VDRL or protein posttherapy, these changes occur slowly and persistent abnormalities are of less concern (47). If the cell count has not decreased after 6 months or is not entirely within the normal reference range after 2 years, the CDC suggests that re-treatment be considered (47).

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented in the medical records and follow-up serologic titer levels have declined appropriately. Penicillin is effective for preventing maternal transmission of syphilis to fetuses and for treating established fetal infection (47). Whether the recommended regimens using penicillin are optimal in pregnancy is unclear (47). Recent reports have demonstrated disconcerting levels of failure to treat mother or prevent transmission (37,44,67). McFarlin et al. (37) demonstrated a high rate of failure with the current recommended therapy to prevent congenital syphilis. A high VDRL titer elevation at the time of diagnosis and unknown duration of infection were significant risk factors for delivery of an infant with congenital syphilis, despite maternal therapy with CDC-recommended regimens. Wendel et al. (67) reported that two thirds of treatment failures occurred during the secondary stage of syphilis. In addition, McFarlin et al. (37) and Sanchez and Wendel (44) noted the occurrence of failures when the mother was treated within the 4 weeks before delivery. Possible explanations for these failures include the altered penicillin pharmacokinetics during pregnancy, resulting in lower serum concentrations of penicillin in mother and fetus (68) and too short a time interval for resolution of fetal infection requiring continued treatment in the neonate (32). As a result of these data, some experts recommend additional therapy with a second dose of penicillin G benzathine at 2.4 million units intramuscularly 1 week after the initial dose in pregnant women with primary, secondary, or early latent syphilis (47). Ultrasonographic signs of fetal syphilis such as hepatomegaly, fetal hydrops, or placentomegaly indicate a greater risk for failure of fetal treatment (47).

Women treated for syphilis after 20 weeks of gestation are at risk for premature labor and fetal distress if treatment precipitates the Jarisch-Herxheimer reaction. The Jarisch-Herxheimer reaction occurs commonly during treatment of primary, secondary, or early latent syphilis. Klein et al. (69) reported in a study of 33 pregnant women that the Jarisch-Herxheimer reaction complicated 100%, 60%, and none of the patients treated for primary, secondary, and latent syphilis, respectively. Characteristically, the reaction presents with fever, chills, myalgia, headache, hypotension, tachycardia, and transient accentuation of cutaneous lesions (70). It typically commences within several hours of treatment and resolves in 24 to 36 hours. In pregnant women, Klein et al. (69) noted that the most common findings were fever (73%), uterine contractions (67%), and decreased fetal movement (67%). Uterine contractions and decreased fetal movement commenced with the onset of maternal fever in nearly all the women who noted uterine contractions (69). In monitored fetuses, fetal tachycardia with decreased variability occurred commonly in association with maternal fever, and transient late decelerations were noted in 30% (69). Although not proven, the mechanism of the Jarisch-Herxheimer reaction probably relates to the cytokine cascade initiated by the host response to the treponemal cell components. No known prophylactic measures against this reaction are available. Thus, some experts recommend sonographic evaluation of the fetus before initiating treatment of early syphilis diagnosed in the last half of gestation (32). If the evaluation results are normal, penicillin therapy can be administered on an ambulatory basis. On the other hand, with an abnormal sonogram evidencing fetal infection, hospitalization for therapy and fetal monitoring is recommended. Sanchez and Wendel (44) have demonstrated that when severe fetal compromise is evident before initiation of treatment in a viable gestation, early delivery with treatment of mother and neonate postdelivery may result in an improved outcome.

Penicillin is the only effective antimicrobial agent for the treatment of syphilis in pregnancy. Thus, in pregnancy there are no alternatives to penicillin for the treatment of syphilis. Doxycycline and tetracycline are contraindicated during pregnancy and erythromycin cannot be relied on to cure an infected fetus because of unpredictable placental transfer (47). Thus, pregnant women who are allergic to penicillin should be desensitized and then treated with penicillin in a dose and duration determined by the stage of syphilis. Similarly, no proven alternatives to penicillin are available for treating neurosyphilis or congenital syphilis. Penicillin is also recommended in HIV-infected patients.

Approximately 3% to 10% of adults in the United States report a history of penicillin allergy. However, only 10% of persons who report a history of penicillin allergy are still allergic (47). Over time, most individuals who experience a severe reaction stop expressing penicillin-specific immunoglobulin E (IgE) and can be treated safely with penicillin (47). Skin testing with the major and minor determinants can reliably identify those patients at high risk for penicillin reactions (47). Although these reagents have been available for more than 30 years in academic centers, unfortunately only the major determinant (penicilloyl poly-l-lysine) and penicillin G are commercially available. Use of these agents alone detects 90% to 97% of allergic patients. Thus, in places where the minor determinants are not available, caution must be used. In places where both major and minor determinants are available, patients whose skin test results are negative can receive conventional penicillin therapy. Patients whose skin test results are positive should be desensitized, although some experts suggest desensitization of patients whose skin test results are negative as well (when minor determinants are not available). Alternatively, those with negative skin test results can be test-dosed gradually with oral penicillin in a monitored setting when treatment for anaphylactic reaction is readily available.

Desensitization can be accomplished orally or intravenously. Oral desensitization (Table 7.20) is thought to be safer, simpler, and easier (47,71). Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur, though rarely (47). The oral desensitization process requires about 4 hours and as reported by Wendel et al. (71) is safe to use in pregnancy. These authors reported that none of the patients managed and treated with long-acting penicillin at intervals of 1 to 3 weeks had a detectable allergic reaction after the second or subsequent injection (66). Immediately after desensitization is completed, the first dose of penicillin should be given. Ziya et al. (72) described an intravenous penicillin desensitization scheme, which uses an intravenous infusion of graduated amounts of penicillin G (72). The procedure is performed in an intensive care unit with staff and equipment for the management of anaphylaxis. Aliquots of 50 mL are infused over 30 minutes, with each successive aliquot containing a tenfold increase in the concentration of penicillin; the first aliquot contains 0.01 U/mL, and the final contains 100,000 U/mL. Treatment is then commenced using a continuous infusion of aqueous penicillin G at 25,000 U per hour for 8 days. Intermittent dosing could result in a need for repeated desensitization and is thus best avoided.

Dose	Penicillin V Suspension (U/mL)	Ml	Units	Cumulative Dose (U)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Source: Wendel GD, Stark BJ, Jamison RB, et al. Penicillin allergy and desensitization in serious maternal-fetal infections. N Engl J Med 1985;312:1229; with permission.

TABLE 7.20. ORAL DESENSITIZATION PROTOCOL FOR PENICILLIN-ALLERGIC PATIENTS WITH POSITIVE SKIN TEST RESULTS

Although serologic responses in some HIV-infected individuals with syphilis may be altered (e.g., titer levels higher than expected, false-negative test results, and delayed appearance of seropositivity), for most patients coinfected with syphilis and HIV, both the nontreponemal the and treponemal serologic tests for syphilis are accurate (47). According to the CDC (47), it appears that HIV-infected patients with syphilis of less than 1 year's duration are at increased risk for neurologic complications and have higher rates of treatment failures. The CDC estimates that the magnitude of these risks is small. Although treatment with penicillin G benzathine at 2.4 million units intramuscularly, as for patients without HIV infection, is recommended for treatment of primary and secondary syphilis in HIV-infected individuals, multiple doses of penicillin G benzathine, as suggested for late syphilis, is recommended by some experts (47). Recently, Rolfs et al. (73) in a multicenter, randomized, double-blind trial compared two treatments for early syphilis in patients with and without HIV infection: 2.4 million units of penicillin G benzathine and that therapy enhanced with a 10-day course of amoxicillin and probenecid. The rates at which chancres and rashes resolved did ot differ significantly according to HIV status or treatment assignment. Serologically defined treatment failures were more common among the HIV-infected patients. The authors concluded that enhanced treatment did not improve the outcomes and that the current CDC recommendations for treating early syphilis appear adequate for most patients, whether or not they have coinfection with HIV (73). In addition, some experts recommend CSF examination in all HIV-infected patients with primary or secondary syphilis (47). HIV-infected patients with latent syphilis should undergo CSF examination before initiating therapy. With a normal CSF examination result, treatment is with penicillin G benzathine at 7.2 million units, as three weekly doses of 2.4 million units each (47).

Penicillin should be used to treat all stages of syphilis in HIV-infected patients. Thus, HIV-infected persons who are allergic to penicillin should be desensitized and treated with an appropriate penicillin regimen.

Congenital syphilis is unusual if the mother received adequate treatment with penicillin early in pregnancy. Infants should be treated for presumed congenital syphilis if they were born to mothers who meet any of the criteria listed in Table 7.21.

Any child suspected of having congenital syphilis (see section on diagnosis congenital syphilis) should have a spinal tap, a complete blood count with platelet count, and long bone x-rays. If these test results are normal, a single intramuscular injection of penicillin G benzathine (50,000 U/kg) should be given. If the assessment results are abnormal or compliance is not ensured, the infant should receive a 10-day course of aqueous crystalline penicillin G at 100,000 to 150,000 U/kg per day, administered as 50,000 U/kg per intravenous dose, every 12 hours during the first 7 days and every 8 hours thereafter, for a total of 10 days, or penicillin G procaine at 50,000 U/kg per dose intramuscularly per day in a single dose for 10 days (47).

■ Untreated syphilis at delivery
■ Serologic evidence of relapse or reinfection after treatment (e.g., fourfold or more increase in nontreponemal antibody titer)
■ Treated with nonpenicillin regimen for syphilis during pregnancy
■ Treated for syphilis ≤1 mo before delivery
■ Did not have a well-documented history of treatment for syphilis
■ Treated for early syphilis during pregnancy with appropriate penicillin regimen, but nontreponemal antibody titers did not decrease fourfold
■ Treated appropriately before pregnancy but had insufficient serologic follow-up to ensure an adequate treatment response and lack of current infection

TABLE 7.21. MATERNAL CRITERIA FOR TREATMENT OF INFANTS WITH PRESUMED CONGENITAL SYPHILIS

CHANCROID

Chancroid, commonly referred to as “soft chancre,” is one of the genital ulcerative diseases caused by sexually transmitted organisms. It is an acute ulcerative disease often associated with inguinal adenopathy (bubo). The causative agent of chancroid is *H. ducreyi.* This bacterium is a small, nonmotile, Gram-negative rod that has a characteristic “chaining” appearance on Gram stain, which results in a “school of fish” appearance. It is a facultative anaerobe with fastidious growth requirements (1). Like gonococci, *H. ducreyi* organisms require an atmosphere with high humidity, increased CO_2 tension, and a temperature of 33°C to 35°C for growth. In addition, it requires hemin for growth.

Epidemiology

Chancroid is a common disease and a major public health problem in many countries in the developing world. In many of these countries, chancroid is endemic and the WHO estimates an annual incidence of 7 million cases (2). Outbreaks of chancroid have also been reported in urban areas of the United States (3,4,5,6 and 7). From 1950 to 1978, there was a marked decrease in the annual incidence of chancroid in the United States (8). This trend dramatically reversed in 1980 and the annual number of reported cases increased to more than 5,000 (9). More recently

and by 1995, less than 1,000 cases of chancroid were reported in the United States, with most being associated with outbreaks in endemic areas in New York City and New Orleans and Jackson, Mississippi (10). By 1998, only 189 cases of chancroid were reported in the United States (11). Although chancroid has become an infrequent STD in the United States, it should be considered in the differential diagnosis of high-risk patients with a painful genital ulcer in these endemic areas.

Prostitutes are felt to be the reservoir of disease in the epidemics that have occurred recently in North America (1). Major risk factors for chancroid include use of crack cocaine and exchange of sex for money or drugs (7,12). The disease is described most commonly in men, particularly in young sexually active men who have a history of recent contact with prostitutes (1,13). Chancroid is more prevalent among lower socioeconomic groups. Uncircumcised men appear to be more susceptible to *H. ducreyi* (1). As many as 10% of patients with chancroid may be coinfected with *T. palladium* or HSV. In addition to their greater prevalence, men are more frequently symptomatic. Asymptomatic women with lesions of chancroid are rarely seen. Whether the presence of asymptomatic lesions in women is the explanation for their perceived lower frequency of chancroid is not proven, but probable. In addition, asymptomatic women may serve as a reservoir for *H. ducreyi* (1). Brunham et al. (14) have estimated that the probability of sexual transmission of chancroid with a single exposure is 0.35 (14).

The importance of chancroid is further demonstrated by the recognition that chancroid is a major cofactor in the heterosexual transmission of HIV and has been strongly associated with increased infection rates for HIV, particularly in Africa (15,16).

Clinical Presentation

The lesions of chancroid are generally limited to genital sites. In men, they are most commonly found in the internal surface of the prepuce and the frenulum, as well as on the labia, clitoris, and fourchette in women. Trauma facilitates the entry of *H. ducreyi* into skin or mucosal surfaces (1,17).

The incubation period of chancroid is 3 to 10 days, with most occurring between 4 and 7 days. At the site of entry, a small papule develops, which is surrounded by a zone of erythema. Within 2 to 3 days, the lesion becomes pustular or vesiculopustular and ulcerates. The classic ulcer of chancroid is superficial and shallow with a ragged edge (Fig. 7.7). The chancre is surrounded by an inflammatory red halo. The base of the ulcer is covered with a necrotic exudate. Unlike the nontender syphilitic chancre, the chancre of chancroid is painful and tender. In addition, it is not indurated (i.e., “soft”). Although only a single ulcer is present in one half of men, multiple ulcers are the rule in women, with Plummer et al. reporting that women have a mean of four and a half discrete ulcers (18). In women, chancroid lesions are predominantly found at the entrance to the vagina involving the fourchette, labia, vestibule, and clitoris (1,18).

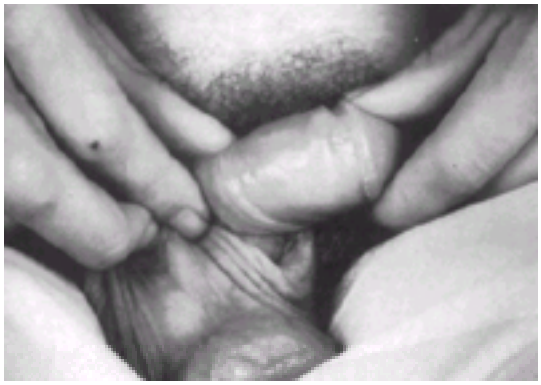


FIGURE 7.7. Chancre of chancroid with red halo and “dirty” necrotic base.

In approximately 50% of cases, a bubo develops. The bubo appears 7 to 10 days after the initial lesion and is characterized by acute, painful, tender, inflammatory inguinal adenopathy. The bubo is unilateral in about two thirds of cases and is unilocular. If untreated, the bubo will rupture, forming a large ulcer in the inguinal area. Bubo formation is less common in women (18).

In men, the usual clinical complaints relate to the ulcerative lesion or tender inguinal adenopathy. Women tend to present with less obvious specific symptoms such as dysuria, rectal bleeding, dyspareunia, or vaginal discharge (1). The combination of a painful ulcer and tender inguinal adenopathy is suggestive of chancroid but only occurs in one third of patients. The presence of a painful ulcer in combination with suppurative inguinal adenopathy is almost pathognomonic for chancroid.

Diagnosis

The diagnosis of chancroid relies on Gram-stained smears, culture, and clinical characteristics of the lesions. A Gram stain of the exudate from the lesion or an aspirate of the bubo may reveal the presence of Gram-negative rods that tend to form chains (Fig. 7.8). The sensitivity of the Gram stain from the lesion or bubo is only 50% (19). A definitive laboratory diagnosis of chancroid depends on the isolation of *H. ducreyi* from the lesion or bubo. However, the organism is fastidious, and isolation of *H. ducreyi* is not routinely performed in most general clinical microbiology laboratories. Thus, in many instances, the diagnosis of chancroid is based on clinical findings and exclusion of the other causes of genital ulcers (e.g., HSV, syphilis, and LGV). Ideally, an attempt should be made to make a definite diagnosis by identifying the causative agent. Gonococcal agar base or Mueller-Hinton agar base supplemented with 0.2% activated charcoal, 1% bovine hemoglobin, 1% CVA enrichment, and 3 mg/mL vancomycin is the preferred media for primary isolation of *H. ducreyi* (19). Growth of *H. ducreyi* is optimized in a water-saturated atmosphere containing 5% to 10% CO_2l and an incubation temperature of 33°C (1). The CDC notes that even with the use of these media, the sensitivity is at most 80% (20). PCR has been shown to compare well with culture, having a sensitivity of more than 95% (10,21). This technology should be commercially available soon. The CDC recommends that a probable diagnosis of chancroid may be made if the following criteria exist: (a) if the individual has one or

more painful genital ulcers; (b) there is no evidence of syphilis by dark-field examination of lesion or by serology performed at least 7 days after onset of ulcers; and (c) either the clinical presentation of the genital ulcers and regional lymphadenopathy are typical for chancroid or test results for HSV are negative (20).

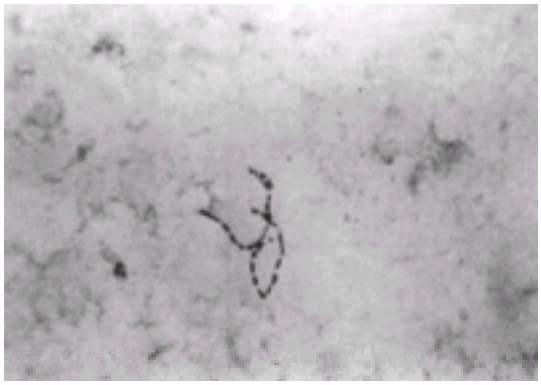


FIGURE 7.8. The “school of fish” appearance of *Haemophilus ducreyi* on Gram stain.

Treatment

Sulfonamides and tetracyclines were the mainstay in the treatment of chancroid for many years. However, frequent reports of clinical resistance occurred (13,22), which have led to extensive changes in the recommended approach to the treatment of chancroid. The current CDC recommendations for the treatment of chancroid are presented in Table 7.22. No instances of antimicrobial resistance by *H. ducreyi* to azithromycin, ceftriaxone, or erythromycin has been reported. The fluoroquinolones are also very effective treatments of chancroid. The CDC suggests that all patients diagnosed with chancroid be tested for HIV infection.

Recommended regimens
Azithromycin 1 g p.o. in a single dose
- or -
Ceftriaxone 250 mg i.m. in a single dose
- or -
Ciprofloxacin[a] 500 mg p.o. b.i.d. for 3 d
- or -
Erythromycin base 500 mg p.o. q.i.d. for 7 d

[a]Contraindicated for pregnant and lactating women.
Source: Centers for Disease Control and Prevention. Centers for Disease Control 2001 sexually transmitted diseases treatment guidelines

TABLE 7.22. TREATMENT OF CHANCROID: 2001 GUIDELINES FOR TREATMENT OF SEXUALLY TRANSMITTED DISEASES CENTERS FOR

Follow-up examination should occur 3 to 7 days after initiation of therapy (20). With successful treatment, symptomatic improvement of the ulcer is present within 3 days and objective improvement within 7 days after therapy. Clinical resolution of fluctuant buboes is slower than that of ulcers and may require needle aspiration (20). Sexual contacts within the 10 days before onset of symptoms should be examined and treated (20).

In pregnancy, ciprofloxacin is contraindicated. The safety of azithromycin has not been established. Thus, ceftriaxone or erythromycin is the preferred regimen for pregnant and lactating women. No adverse effects of chancroid on pregnancy outcome or on the fetus have been demonstrated (20).

Lymphogranuloma Venereum

LGV is an STD caused by *C. trachomatis,* serotypes L_1, L_2, and L_3 (1). These LGV strains of *Chlamydia* are easily differentiated from other *C. trachomatis* strains by antigenic structure and because they are much more invasive in tissue culture systems (2). The disease is manifested by both generalized systemic symptoms and a wide spectrum of anogenital lesions, lymphadenopathy, and gross devastation of perineal tissue (2). LGV is uncommon in the United States. It usually presents as inguinal adenopathy, because the painless genital ulcer stage of the disease often goes unnoticed.

Epidemiology

Although LGV is worldwide in distribution, it most commonly occurs in tropical areas. LGV is endemic in East and West Africa, India, parts of Southeast Asia, South America, and the Caribbean (3,4). On the other hand, it is a sporadic disease in North America, Europe, Australia, most of Asia, and South America (4).

Approximately 350 cases per year are reported in the United States. Most acute LGV cases are in men with a male to female ratio of 5 : 1 or greater (5). Schachter (5) suggested this sex differential is due to patterns of pelvic lymph drainage, which in women results in deep iliac adenopathy that is not apparent, rather than the inguinal adenopathy seen commonly in men (5). On the other hand, long-term complications such as ulceration, genital hypertrophy, and rectal strictures are most common in women (6,7). As is true for other STDs, LGV is more common in urban settings, among the sexually promiscuous, and among lower socioeconomic classes (4). Although transplacental congenital infection has not been reported, acquisition during passage through an infected birth canal can occur (4).

Clinical Presentation

LGV is primarily an infection of lymphatic tissue characterized by thrombolymphangitis and perilymphangitis, in which inflammation spreads from

infected lymph nodes into the adjacent tissue (4). The lymph nodes draining the infected site enlarge, necrose, and form abscesses, which coalesce and rupture, thereby leading to fistula formation and sinus tracts (4). Healing occurs secondary to fibrosis, which results in obstruction of lymphatic vessels, chronic edema, and enlargement of affected anatomic locations. It is believed that most of the tissue damage associated with LGV is caused by a cell-mediated “hypersensitivity” to chlamydial antigens (4).

The clinical presentation of LGV is divided into primary, secondary, and tertiary stages. After an incubation time that ranges from 3 to 21 days, the primary lesion develops in the genital area. In men, the primary lesion usually occurs on the coronal sulcus, whereas in women, the most common site is the posterior vaginal wall, followed by the fourchette, cervix, and vulva. This primary lesion is vesicular or papular and painless; it may ulcerate but heals within a few days without scarring. The primary lesion generally is not appreciated or recognized by patients. An exception is primary rectal LGV, which manifests as proctitis with diarrhea, discharge, and ulceration (8).

The secondary stage of LGV is characterized by acute lymphadenitis with bubo formation (inguinal syndrome) or acute hemorrhagic proctitis (anogenitorectal syndrome). The secondary stage of inguinal adenopathy develops 1 to 4 weeks after the primary lesion. This invasive stage of LGV is often preceded by the onset of systemic symptoms such as fever, malaise, headache, and myalgia (4,9). Inguinal adenopathy is the most frequent clinical manifestation of LGV (2). The adenopathy is unilateral in two thirds of cases and begins as firm, discrete multiple nodes that are slightly tender. Over the next week or two, a more extensive adenitis commences as the nodes become matted together and become adherent to the subcutaneous tissue and overlying skin. The skin often is discolored, and the lesion becomes very painful. The horizontal group of superficial inguinal nodes is most commonly involved, but the femoral nodes may also be affected. If both groups become involved, the inguinal ligament creates a groove between the node groups, producing the “groove sign,” which occurs in 10% to 20% of LGV cases (Fig. 7.9) and is felt to be pathognomonic for LGV. The matted mass proceeds to suppurate, and multiple draining sinuses arise from the necrotic lymph nodes. Approximately one third of inguinal buboes in LGV become fluctuant and rupture. In the anogenitorectal syndrome, proctocolitis and hyperplasia of intestinal and perirectal lymphatic tissue occur. This form of secondary LGV is found predominantly in women and homosexual men (10). Symptoms include anal pruritus, mucous rectal discharge, fever, rectal pain, and tenesmus (4).

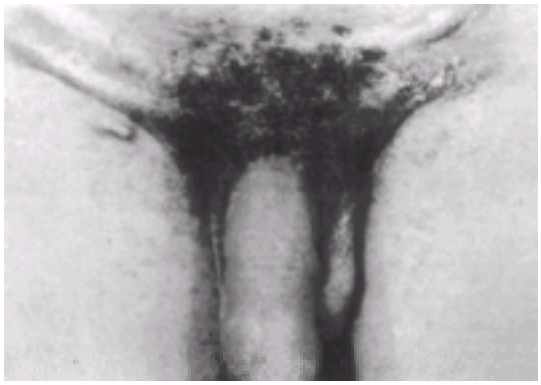


FIGURE 7.9. The grooved nodes (saddle nodes) that are characteristic of lymphogranuloma venereum due to the L_1, L_2, and L_3 strains of *Chlamydia trachomatis*.

The tertiary stage involves the external genitalia and anorectal areas. It is characterized by progressive tissue destruction and extensive scarring. Particularly in women, this phase of disease may be the initial clinical manifestation for which the patient seeks care. This stage may present as hypertrophic ulceration and elephantiasis. Hypertrophic lesions are more common among women, but elephantiasis occurs in both men and women. Sinuses, fistula tracts, and ultimately strictures may occur in the vulva, perineum, or rectum. Stricture formation follows within a few months to 10 years after acute anogenitorectal disease (2).

Diagnosis

LGV occurs with multiple, variable presentations, and no single pathognomonic lesion exists. Thus, diagnosis solely on clinical grounds is, at best, difficult. The diagnosis of LGV can be made by isolation or identification of the chlamydial organism or with the use of serology. Schachter et al. (11) reported that aspiration and culture results of pus from fluctuant nodes were positive in approximately 50% of cases. With the introduction of PCR detection of chlamydiae into clinical practice, amplification methods may become the test of choice (4).

The Frei intradermal test was for many years the backbone of diagnostic efforts for LGV. A positive Frei test result is not evidence of active infection but only indicates previous LGV infection. Moreover, the Frei antigen is common to all chlamydiae, so the specificity of a positive Frei test result is poor for LGV, which limits its clinical usefulness.

The most commonly used diagnostic test for LGV today is the complement-fixation test for *Chlamydia* sp antibodies. This test is very sensitive, and titer levels greater than 1 : 64 are considered diagnostic. However, complement-fixation titers are present with mucosal infections due to other chlamydial subgroups, although usually at lower titer levels (12). The microimmunofluorescence test of Wang and Grayston can be used for typing isolates of *Chlamydia* and thus can identify the chlamydia biovars responsible for LGV. However, the microimmunofluorescence test is available in a limited number of research laboratories.

Treatment

As recommended by the CDC (Table 7.23), doxycycline (100 mg orally twice a day for 21 days) is the therapy of choice for LGV (13). An alternative regimen is erythromycin (500 mg orally four times a day for 21 days). Although the activity of azithromycin against *C. trachomatis* suggests it would be effective in multiple doses over 2 to 3 weeks, no clinical studies have been reported (13). In pregnant or lactating women, the erythromycin regimen should be used. Sexual contacts of a person with LGV within 30 days before the onset of symptoms should be examined,

tested for urethral or cervical chlamydial infection, and treated. Fluctuant inguinal nodes should be aspirated to prevent sinus tract formation. Incision and drainage or surgical extirpation of nodes is contraindicated, because such intervention will delay healing and may further obstruct lymphatic drainage. Late sequelae such as strictures and fistulae may require surgical intervention (13).

Recommended regimen
Doxycycline 100 mg p.o. b.i.d. for 21 d
Alternative regimen
Erythromycin 500 mg p.o. q.i.d. for 21 d

Source: From Centers for Disease Control and Prevention. Centers for Disease Control 2001 guidelines for treatment of sexually transmitted diseases.

TABLE 7.23. TREATMENT OF LYMPHOGRANULOMA VENEREUM

DONOVANOSIS (GRANULOMA INGUINALE)

Donovanosis (granuloma inguinale) is a chronic progressively destructive infection of the genital area caused by the bacterium *Calymmatobacterium granulomatis.* This organism is a Gram-negative, nonmotile, nonsporing, encapsulated rod and is grouped with Enterobacteriaceae because it cross-reacts with *Klebsiella* and *Escherichia coli* (1,2). Previously the disease was called granuloma inguinale. The presence of Donovan bodies characterizes this infection (Fig. 7.8). Although *C. granulomatis* does not grow on cell-free media, it has been cultured in chicken embryonic yolk sac (1).

Epidemiology

Donovanosis is most common in Papua New Guinea, southern Africa, northeast Brazil, French Guyana, and aboriginal tribes in Australia (3). The disease is very rare in temperate climates, and less than 100 cases are reported annually in the United States (1,3).

The variable incubation time and initial subtle clinical findings have confused the epidemiology of donovanosis (2). Although it is generally believed that donovanosis is an STD, its exact mode of transmission is still not clearly understood. Young children and very old adults without sexual activity also develop the infection.

The sexually transmitted hypothesis is supported by various evidence (2,4). They include the following: (a) Most lesions occur on the genitalia; (b) the disease occurs most frequently in the sexually active age-group; (c) there is almost always a history of sexual exposure before the appearance of the ulcer; (d) other STDs are present

among patients with donovanosis; and (e) donovanosis has been proven to exist in more than 50% of the sex partners of patients with the disease. An alternative hypothesis has been championed by Goldberg (5), who suggests that donovanosis is not necessarily an STD, and the habitat of *C. granulomatis* is the intestinal tract. The transmission can be nonsexual or sexual, and autoinoculation associated with trauma may be a more important mode of transmission than sexual activity. He points to the antigenic similarity between *C. granulomatis* and Enterobacteriaceae and the occasional cases that occur in the very young or older adult patients with recent sexual activity for support of the second concept.

Clinical Presentation

Donovanosis is a low-grade chronic infection whose communicability is low, and repeated close physical contact seems to be necessary for transmission (2). The incubation period varies from a few days to a few months (1). The disease has a very insidious onset, and the earliest lesion presents as a papule or nodule that is painless and often not noticed by patients. Most cases (90%) involve the genitalia, with the inguinal region being the site in 10% (3). In women, the usual sites are the labia and fourchette. The epithelium overlying the lesion subsequently ulcerates, producing an enlarging granulomatous beefy red, velvety ulcer. If untreated, the lesions may spread to involve the inguinal regions, producing the “pseudobubo.” However, despite extensive disease, there is a characteristic absence of adenopathy in the inguinal region. The pseudobubo is a subcutaneous granulomatous process, rather than adenopathy. Rarely, lymphatic obstruction and fibrosis occur. Unless secondarily infected, the lesions of granuloma inguinale are painless. O'Farrell (6) has reported that donovanosis has a more aggressive course during pregnancy.

Diagnosis

The diagnosis of donovanosis is usually made on clinical grounds because of the characteristic granulomatous process. *C. granulomatis* is very fastidious and has been successfully cultured only in embryonated hens' eggs. Thus, the diagnosis is not made by culture, but with histologic identification of *C. granulomatis.* Diagnosis may be confirmed by a stained smear of a crushed tissue preparation or biopsy of the lesion. The smear is stained with Giemsa or Wright stain. Tissue sections are stained with Giemsa or silver stains for visualization of the organisms (3). Donovan bodies in macrophages on the smear or biopsy must be demonstrated to make a certain diagnosis (Fig. 7.10). No serologic tests are available for donovanosis.

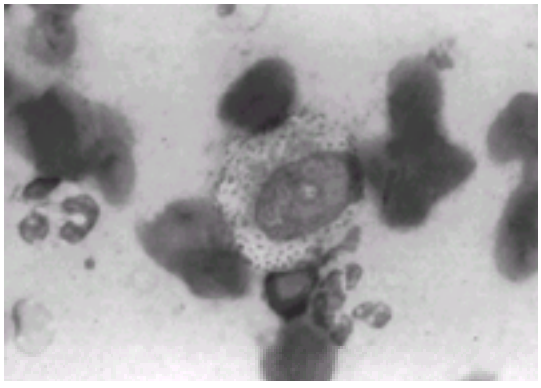


FIGURE 7.10. *Calymmatobacterium granulomatis* (commonly known as Donovan body), the etiologic agent of granuloma inguinale.

Treatment

The CDC proposes either trimethoprim-sulfamethoxazole or doxycycline given over a minimum of 3 weeks as the recommended agents for the treatment of donovanosis (Table 7.24) (7). Alternative agents include ciprofloxacin or erythromycin base for a minimum 3-week course. Addition of gentamicin (1 mg/kg intravenously every 8 hours) should be considered if lesions fail to respond in the first few days of therapy (7). Therapy should be continued until the lesions are completely healed.

Recommended regimens
Trimethoprim-sulfamethoxazole one double-strength tablet p.o. b.i.d. for a minimum of 3 wk
- or -
Doxycycline 100 mg p.o. b.i.d. for a minimum of 3 wk
Alternative regimens
Ciprofloxacin 750 mg p.o. b.i.d for a minimum of 3 wk
- or -
Erythromycin base 500 mg p.o. q.i.d. for a minimum of 3 wk
- or -
Azithromycin 1g p.o. once per week for at least 3 weeks

TABLE 7.24. TREATMENT OF DONOVANOSIS (GRANULOMA INGUINALE) 2001 GUIDELINES FOR TREATMENT OF SEXUALLY TRANSMITTED DISEASES CENTERS FOR DISEASE CONTROL AND PREVENTION

Sex partners should be examined and treated if they had sexual contact in the 60 days preceding the onset of symptoms and have clinical signs and symptoms of the disease. In pregnancy and during lactation, the erythromycin regimen is recommended and the addition of parenteral gentamicin should be given strong consideration (7).

ECTOPARASITES

Scabies

Human scabies is caused by the itch mite, *Sarcoptes scabiei.* This mite is 400 µm long and has four pairs of legs; the front two have suckers, whereas the rear two end in bristles (1). The female is more often seen and is larger. *S. scabiei* moves briskly across the skin at 2 to 5 cm per minute and can travel from the neck to the wrist in a

few hours (1). Mites are best seen with a hand lens.

The adult female excavates a burrow in the skin, which is where fertilization takes place and makes her fertile for life. After fertilization, the female emerges and excavates a new burrow, which she extends by 0.5 to 5.0 mm per day as she begins laying two to three eggs per day. The eggs hatch in 3 to 4 days, and the larvae emerge from the burrow and dig into adjacent skin where three moltings occur before adulthood is achieved. Females live up to 6 weeks, but adult males are short lived.

Epidemiology

Scabies is common throughout the world and appears in epidemics at 10- to 30-year intervals (2,3 and 4). It is more common in men than women and in Whites than Blacks.

Scabies is now considered an STD, and close and prolonged contact with an infested person is a prerequisite for transmission. Unlike other STDs, the disease is also spread by nonsexual contact; close person-to-person contact, as with crowded living conditions or sharing a bed, can be responsible. The role of fomites in transmission is possible, but the risk with contaminated clothing and bed linen is small (5). Unlike most STDs, which may be spread by brief sexual encounters, scabies is more likely to be transmitted by sharing a night in bed (3,6).

Clinical Presentation

Scabies manifests itself with a pruritic, pleomorphic rash that has an insidious onset and a characteristic pattern of involvement that includes wrist, finger webs, elbows, axillae, genitalia, and buttocks (1). Initial infestations are clinically latent for 4 to 6 weeks after acquisition of scabies. Patients report a gradual onset of pruritus and rash over 3 to 4 weeks after initial infestation (3). With repeated infestations, the onset of symptoms is relatively prompt, within hours. Much of the symptomatology of scabies is the result of the host immune response to *S. scabiei* (3).

Pruritus is the predominant symptom and may be intense. Typically, the itching is worst at night. The physical findings in scabies include the presence of the burrows, a papular erythematous rash, and persistent pruritic nodules (1). The burrows are 5 to 10 mm long, and the organism may be seen as a tiny brown and white speck at the inner end.

Diagnosis

The burrow of scabies is pathognomonic. It is a short, wavy, dirty-appearing line that often crosses skin lines and is most commonly located on finger webs, volar wrists, and elbows (3). Use of a magnifying glass is sufficient and the burrows can be more easily seen after ink staining (3). However, they are not apparent in many cases of scabies infestation. Most sites also contain small, erythematous, excoriated papules (3). Confirmation of the diagnosis is made by identifying the mite, eggs, or fecal pellets from burrows on microscopic examination. Fresh lesions should be used for obtaining mites. The preferred laboratory technique for microscopic identification of scabies is skin scrapings (3). Alternative methods include needle extraction of the mite, epidermal shave biopsy, burrow ink test, curettage of burrows, swab technique

with clear cellophane adhesive, or punch biopsy (3).

Scabies is called the great imitator because patients can present with various lesions. Thus, many dermatologic conditions must be considered in the differential diagnosis (1,2,3,4,5 and 6). These include eczema, acute urticaria, impetigo, erythrasma, insect bites, neurodermatitis, and dermatitis herpetiforms. However, the history of insidious onset and the presence of nocturnal pruritus, pleomorphic lesions, and the characteristic distribution of lesions should strongly suggest scabies. Presence of itching in family members also indicates a high likelihood of scabies.

Treatment

Successful treatment of scabies necessitates correct application of an effective scabicide to the patient, sexual contacts, and family members. The current CDC-recommended regimen for the treatment of scabies is permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8 to 14 hours (7). Alternative regimens include lindane (Kwell) (1%) at 1 oz of lotion or 30 g of cream applied thinly to all areas of the body from the neck down and washed off thoroughly after 8 hours or sulfur (6%) precipitated in ointment applied thinly to all areas nightly for three nights (7). Previous applications should be washed off before new applications are applied (7). Thoroughly wash off the sulfur 24 hours after the last application (7).

Although permethrin has been demonstrated to be safe and effective, it is more costly than lindane (7). However, lindane resistance has been reported in some areas of the United States and other countries of the world (7). Moreover, seizures have occurred when lindane has been applied after a bath or used in the presence of extensive dermatitis (7). Aplastic anemia after lindane use has also been reported (7). Thus, it is recommended that lindane not be used after a bath or by persons who have extensive dermatitis (7).

Pregnant and lactating women should not be treated with lindane; permethrin is recommended for the treatment of scabies in pregnant or lactating women (7). The patient should be instructed that continued lesions and pruritus may occur, even though the mites and eggs have been killed. However, if no clinical improvement is noted, a second application after 1 week is indicated.

The CDC suggests that ivermectin as a single oral dose of 200 mg or 0.8% topical solution is a potential new therapeutic modality. Meinking et al. (8) demonstrated that a single oral dose of 200 mg of ivermectin is highly effective and safe in the treatment of scabies in both immunocompetent and immunocompromised patients. However, it is not approved by the Food and Drug Administration. Once available, it will be the first highly efficacious, inexpensive, and safe oral agent for the treatment of scabies (9). Advantages of oral ivermectin include (a) assurance of compliance, (b) facilitation of control of outbreaks in institutions, (c) more rapid clinical response of pruritus, and (d) effectiveness in immunocompromised persons with severe skin manifestations of scabies (9).

At the conclusion of therapy, the patient's underwear, nightclothes, sheets, and pillowcases should be decontaminated either by machine washing or machine drying

using the hot cycle or by removing them from body contact for 72 hours or more (7).

Sex partners and close household contacts should be treated as described earlier. If no clinical improvement is noted, a single re-treatment after 1 week is appropriate. Clothing and bed linen used within the previous 2 days should be washed and dried by machine (hot cycle) or dry-cleaned.

Immunocompromised and HIV-infected patients are at increased risk for Norwegian scabies (crusted scabies), a disseminated dermatologic infection (7). This form of scabies is characterized by exuberant scaling lesions that are heavily infected with mites (3). These patients can infect via casual contact (3). Treatment may require antibiotics and supportive care, in addition to repeated courses of specific treatment with scabicides (3).

Pediculosis Pubis

Pthirius pubis, the crab louse, is the responsible etiologic agent for pediculosis pubis. Similar to other STDs, this infestation has also been increasing, and it is estimated that 3 million cases of pediculosis are treated each year in the United States. Infestation by the crab (or pubic) louse should be considered in any patient complaining of groin irritation or pruritus. The organism is 1 to 2 mm long, grey, tough skinned, and square. It has six pairs of legs, of which the last two pairs are adapted for grasping suitably spaced hairs. Crab lice move relatively slowly, about 10 cm per day (1,2 and 3).

Twenty-four hours after mating, the female begins to lay eggs at a rate of approximately four per day. The eggs are attached to a hair near its root. After an incubation time of 7 days, a nymph is hatched, which proceeds through three molts over 8 to 9 days. Once the louse reaches sexual maturity, the adult expectancy of life is 3 to 4 weeks (1).

Epidemiology

Although acquisition of *P. pubis* is nearly always through sexual contact, it may be spread through fomites. Pediculosis pubis is more contagious than any other STD, with a 95% chance of contracting the disease with a single sexual encounter (2). Pediculosis pubis is most commonly encountered during adolescence and young adulthood; from ages 15 to 19, it is more common in women, whereas after 20 years of age, men are more commonly infected (3).

Clinical Presentation

The incubation time of pediculosis is 30 days. Patients present with irritation or pruritus secondary to bites. The intense itching is believed to be due to allergic sensitization (2). On occasion, patients may see the crab louse moving over the skin. Distribution involves the pubic, perineal, and perianal regions. With bites by many lice over a short period, systemic manifestations such as mild fever, malaise, or irritability may occur.

Diagnosis

Visualization of lice, larvae, and nits with the use of a magnifying glass is diagnostic for pediculosis pubis. Microscopic examination will reveal the typical crablike morphology.

Treatment

The recommended treatment regimens for pediculosis pubis include permethrin (1%) creme rinse applied to affected area and washed off after 10 minutes, pyrethrin with piperonyl butoxide applied to affected area and washed off after 10 minutes, or lindane (Kwell) 1% shampoo applied for 4 minutes to the affected area and then thoroughly washed off. Lindane is not recommended for pregnant or lactating women. After either treatment, combing the infested areas with a fine-tooth comb facilitates removal of remaining lice and nits. Lindane is the least expensive therapy. Toxicity (e.g., noted by seizures and aplastic anemia) has not been reported when treatment is limited to recommended 4-minute periods.

Re-treatment is indicated after 7 days if lice are found or eggs are observed at the hair-skin junction. Clothing or bed linen that may have been contaminated within the last 2 days should be washed and dried on hot cycle or dry-cleaned. All sexual partners, family members, and close contacts must be treated at the same time, even if asymptomatic.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a viral skin infection of children and young adults. The Molluscum contagiosum virus has recently been designated as a new poxvirus genus Molluscipoxvirus containing double-stranded DNA. Like other poxviruses, its life cycle consists of cytoplasmic replication, prominent inclusion bodies, and cytopathic hyperplasia (1). Characteristic small, firm, umbilicated papules occur on the extremities or trunk and in sexually transmitted cases, in the genital area. Examination of infected cells reveals the pathognomonic molluscum bodies, which are ovoid accumulations of maturing virions (2).

Epidemiology

Molluscum contagiosum is transmitted by skin-to-skin contact, fomites, and autoinoculation. The incubation period averages 2 to 3 months and ranges from 1 week to 6 months. As noted by Brown et al. (1), there are two major forms of molluscum contagiosum. The childhood disease, which affects the face, trunk, and limbs, is transmitted by skin contact and fomites. Disease affecting young adults is sexually transmitted, occurs in the genital area, and is usually acquired by skin contact during sexual intercourse. Cases of molluscum contagiosum appear to be increasing in frequency in the United States and United Kingdom (1,3). Reports before the onset of the AIDS epidemic demonstrated that molluscum contagiosum cases had quadrupled in the United Kingdom from the early 1970s to the 1980s and increased 11-fold in U.S. surveys of private physicians between 1966 and 1983 (4,5). Since the mid-1980s, emphasis has focused on the frequency of infection in patients

with AIDS, with rates of 5% to 18% (6).

Clinical Presentation

Molluscum contagiosum affects normal skin, rather than mucous membranes. The characteristic dome-shaped papules with central umbilication develop slowly and remain stable for long periods. Lesions are multiple, but generally less than 20 appear. The lesions are usually flesh colored but may be grey-white, yellow, or pink.

The disease is usually asymptomatic, but on occasion, pruritus may be present. The usual life of a lesion is less than 2 months, but they can last for several years. Most commonly, the crop of molluscum contagiosum lesions tends to be self-limited and lasts 6 to 9 months (1).

Diagnosis

Examination reveals the characteristic smooth, light-colored papules with an umbilicated center. They are usually multiple and have the distribution noted earlier for either childhood disease or sexually transmitted forms. To confirm the diagnosis, if it is in doubt, microscopic examination can be performed. Either the lesion can be squeezed to express the white caseous material from its core or the lesion may be curetted off. The specimen is then crushed on a slide and stained with Gram, Wright, or Giemsa stain. The cells will reveal the pathognomonic large intracytoplasmic molluscum bodies (2).

Treatment

Molluscum contagiosum is a benign and self-limited disease. Although lesions often resolve spontaneously, treatment may shorten the duration of lesions and result in decreased autoinoculation or transmission. Several alternative therapies are available (1). A small superficial incision on the top of the lesion may be made, and the contents are then removed with a comedo extractor. Curettage of the lesion, followed by cautery, is effective. For multiple lesions, freezing with liquid nitrogen has been successful. Sexual partners should be examined and treated as well.

GENITAL HUMAN PAPILLOMAVIRUS INFECTIONS

HPV infections are members of the Papovaviridae family, are composed of double-stranded DNA, and have a molecular weight of 5×10^6 daltons (1). The papilloma viruses are highly host specific (1,2). These viruses are characterized by an ability to infect and transform epithelial cells (2). To date, with the use of recombinant DNA technology, more than 100 types of HPV have been identified; of these, at least 35 primarily infect epithelium of the genital tract (3,4 and 5). HPV types are associated with both anatomic sites of infection and biologic behavior (Table 7.25) (6,7). As noted by Koutsky and Kiviat (8), HPVs are epitheliotropic and viral replication requires the presence of differentiating squamous epithelium. HPV types are defined according to their DNA genotype on the basis of alignments of nucleotide sequences of the open reading frames (ORFs) L1, E6, and E7 (5,9).

Clinical Manifestations	HPV Types
Skin lesions	
Plantar warts	1, 2, 4
Common warts	2, 4, 26, 27, 29, 57
Flat warts	3, 10, 28, 49
Butcher's warts	7
Benign echovirus (EV) lesions	2, 3, 10, 12, 15, 19, 36, 46, 47, 50
EV (benign or malignant)	5, 8, 9, 10, 14, 17, 20–25, 37
Nonwarty skin lesions	37, 38
Genital	
Condyloma acuminata	6, 11, 42–44, 54
Noncondylomatous lesions and/or cervical intraepithelial neoplasia	6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 40, 42, 43, 51, 52, 55, 56, 57–59, 61, 62, 64, 67–70
Carcinoma	16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56, 66, 68
Nongenital mucosal	
Mouth (focal epithelial hyperplasia)	13, 32
Laryngeal papilloma	6, 11, 30
Maxillary sinus papilloma	57
Carcinoma (head/neck/lung)	2, 6, 11, 16, 18, 30

TABLE 7.25. CLINICAL MANIFESTATIONS ASSOCIATED WITH DIFFERENT HUMAN PAPILLOMAVIRUS (HPV) TYPES

Genital warts have been described since the first century ad (8,10,11). The infectious nature of these lesions was first appreciated at the end of the nineteenth century and the viral etiology of genital warts, as well as that of common skin warts, was demonstrated in 1907 (8,11). Since the work of Barrett et al. (12) in the 1950s, the sexual route of transmission for genital warts and other genital HPV infections has been generally accepted. Although the cytologic findings now recognized as characteristics of cervical HPV infection were initially described in 1956 (13), these cellular changes were not determined to be caused by HPV infection until the mid-1970s (14,15). During the 1980s and 1990s, multiple epidemiologic and molecular studies demonstrated the link between some HPV types and the development of anogenital cancers (8,11,16). More recently, it has been demonstrated that HPV DNA is present in more than 90% of squamous carcinomas of the anogenital tract (11,16,17 and 18). In addition, perinatal transmission of HPV has been demonstrated.

The common genital HPV types can be divided into two major categories based on their oncogenic potential: high-risk types and low-risk types (Table 7.26) (19,20,21,22,23,24,25,26,27 and 28). Some authorities also include a third intermediate category (20,29). HPV types in the low oncogenic risk group include types 6, 11, 42, 43, and 44. They are associated with genital warts, condyloma, and some cases of low-grade squamous intraepithelial lesions (SILs) but rarely in invasive cancers. The high oncogenic risk group includes HPV types 16, 18, 20, 31, 45, 45, 54, 55, 56, 64, and 68. These high-risk types are commonly detected in women with high-grade SILs and invasive cancers. The most common oncogenic HPV types are 16, 18, 45, and 56. In the intermediate risk group are HPV types 33, 35, 39, and 51. Although these types are associated with high-grade SILs, they are rarely detected in invasive carcinomas.

Low risk
HPV-6, -11, -42, -43, -44
Intermediate risk
HPV-33, -35, -39, -52, -58
High risk
HPV-16, -18, -26, -31, -45, -54, -55, -56, -64, -68

TABLE 7.26. THE RISK FOR MALIGNANCY POTENTIAL AMONG COMMON GENITAL HUMAN PAPILLOMAVIRUS (HPV) TYPES

Pathogenesis

Genital warts (clinical and subclinical) have been associated with HPV types 6, 11, 16, 18, 31, 33, 35, and 39 (30,31). HPV types 6 and 11 are the most prevalent viruses associated with exophytic warts (condyloma acuminatum) (19,30,31 and 32). On the other hand, HPV types 16 and 18 are most frequently associated with genital neoplasia (30,31,33,34). It is important to recognize that most HPV infections with low- and high-risk types occur in the absence of external genital warts, squamous intraepithelial neoplasia, or malignancy (35,36,37 and 38).

All known HPVs have a similar structural and genomic organization. HPVs are nonenveloped virions containing a double-stranded circular DNA genome of 7,800 to 7,900 base pairs and an icosahedral capsid (29). Application of molecular biologic techniques in the analysis of HPV has identified classes of viral genes and provided information about the differences between the replication and expression of virus in benign and malignant tissue. The viral genome is organized into three major regions. There are two protein-encoding regions (early and late gene regions) and a noncoding upstream regulatory region (URR) (29,39). The URR controls transcription of the early and late regions and as a consequence regulates production of viral protein and infectious particles (ORF), which are transcriptional units that encode for proteins and are designated E1, E2, E4, E5, E6, and E7 (29). Early region gene expression controls replication, transcription, and cellular transformation of viral DNA. In addition, it plays a role in unregulated cellular proliferation. The gene products encoded by E1 and E2 ORFs are critical for viral replication. Although E6 and E7 ORFs also encode proteins critical for viral replication, they also encode proteins critical for host cell immortalization and transformation. The late gene region contains two ORFs (L1 and L2), which encode structural proteins critical to the production of viral capsid (29).

Acute HPV infection of the genital tract probably occurs when microtrauma allows the virus to enter the skin or mucosa of the genital tract (11). The virus enters cells at the basal layer of the epithelium and matures as it passes through the parabasal, spinous, and granular layers of epithelium (11). It is at the granular level that viral DNA replication, late region protein synthesis, and viral particle assembly occur.

Bristow and Montz (29) have noted that after acute HPV infection, three clinical sequelae potentially can occur. Firstly, latent viral infection occurs when the HPV genome is stabilized as a nonintegrated episome and remains in host cells without causing any clinical or morphologic changes in the squamous epithelium of the genital tract. Thus, with latent infection, patients display no clinical evidence of infection but still harbor HPV as demonstrated by DNA detection methodology. Secondly, active infection may occur, which manifests by proliferation of squamous epithelial cells into benign tumors (such as genital warts and condyloma). This occurs when HPV undergoes vegetative replication. Thirdly, high-risk oncogenic types of HPV, which are associated with high-grade lesions, can become integrated into the host genome. Viral integration results in loss of control of proliferation by several critical oncoproteins or tumor suppressors.

With benign lesions such as genital warts, the viral replication of DNA and the expression of viral RNA occur predominantly in the differentiated layers of the epidermis. In genital warts, the viral DNA is an episome and not integrated into the host DNA. Major changes take place as lesions become dysplastic or invasive (40). Viral gene expression occurs in the proliferating layers of the epidermis. Viral DNA is now integrated into the host genome and thus can be transferred to progeny cells. In 80% of cervical malignancies, the HPV genome is integrated into host genome (41). Deletion of late viral genes, which encode the structural viral proteins, occurs. Among the early viral genes, those that play a role in abnormal growth of cells (E6 and E7) continue to be expressed while there is a loss of those early viral genes (E1 and E2) that have a negative effect on the expression of growth-promoting genes. As a result of these events, dysplastic and malignant lesions tend not to produce virus-like particles.

The use of molecular biology has provided insight into the biologic differences between the low-risk HPV types and the high-risk HPV types. Whereas high-risk HPVs induce immortalization of cultured human keratinocytes, low-risk HPVs do not (40). Transformation to a malignant phenotype requires activation of oncogenes or inactivation of tumor suppressor genes (42,43,44,45 and 46). Immortalization by the high-risk HPVs requires the viral genes, E6 and E7. These are the early genes of HPV that are retained and expressed in cervical cancer (46). The E6 and E7 proteins enhance cell growth by, at least in part, inactivating cellular proteins encoded by tumor suppressor genes (39). The inactivated proteins are p53 and retinoblastoma (RB) for E6 and E7, respectively.

The HPV E2 gene product not only functions in normal transcriptional regulation but because the E2 transcript is frequently disrupted, the E2 ORF is also the most significant site for integration of HPV into the host genome (47). As a result, the normal regulatory function of E2 is lost, resulting in overexpression of the oncoproteins E6 and E7 with inactivation of the cellular tumor suppressor gene products p53 and RB, respectively (47). Loss of p53 and RB function is felt to be required for the uncontrolled cellular proliferation and growth present in squamous cell cancers (29). Virtually all squamous cell cancers of the genital tract contain and express E6 and E7 (29). Moreover, *in vitro* transcription studies have demonstrated that E6 and E7 are required for cell transformation and oncogenesis (48). Lung et al. (49) noted that in HPV-16 and -18–infected cells, the E6 protein binds to p53, resulting in degradation of the p53 tumor suppressor gene and loss of p53 activity. Reduction in p53 levels leads to unregulated cell progression and accumulation of genetic mutations. Interestingly, the E6 protein encoded by high-oncogenic-risk HPV

types (e.g., 16 and 18) has a greater affinity for p53 or accelerates p53 degradation when compared with E6 protein associated with low-oncogenic-risk HPV types (e.g., 6 and 11) (50,51).

The E7 gene encodes a protein that binds to the RB protein (52). In normal cells (not infected with high-oncogenic-risk HPV), the RB proteins form complexes with transcription factors of the E2 family during early phases of the cell cycle (53,54). These complexes negatively regulate cell growth by repressing transcription of E2-dependent genes (53,54). As infected cells progress further into the cell cycle, the E2-RB complex dissociates, releasing free E2, which stimulates transcription of the E2-dependent genes and permits DNA replication to occur. The E7 protein produced by high-oncogenic-risk HPV types binds to RB protein, disrupting the E2-RB complex, and alters the normal cellular growth control mechanism (55). Consequently, the released free E2 stimulates transcription of genes required for DNA replication. Similar to what is seen with E6, the E7 protein binds with greater affinity to RB in high-oncogenic-risk HPV types than in low-oncogenic-risk HPV types (29).

Epidemiology

It is estimated that at least 24 million Americans are infected with HPV and that between 500,000 and 1 million new cases of HPV-induced genital warts occur each year in the United States (56,57 and 58). Clinically evident genital warts cases (condyloma acuminatum) continue to occur in epidemic proportions (57). In the United States, there was an eightfold increase in the incidence of genital warts reported from the early 1950s to the late 1970s (13 per 100,000 to 106 per 100,000) (59). Not only was this dramatic increase seen in STD clinics (60), but a survey of private physician practices in the United States demonstrated a 450% increase in the number of consultations for genital warts in the 15 years before 1984 (61,62). Gall (11) recently suggested that there has been a tenfold increase in HPV-related cases in STD clinics and in private physician offices. The CDC estimated in 1983, there were twice as many office visits for genital warts as there were for genital herpes, with 1,100,000 visits for genital warts (62). Thus, genital warts is the most common viral STD, and in some STD clinics, it is the third most common STD, after gonorrhea and chlamydia (63). In 1995, genital warts accounted for more than 240,000 initial physician office visits (58). The IOM estimates that the economic burden of HPV in the United States exceeded $3.8 billion in total costs in 1997 (excluding costs for HPV-related cervical cancer).

Because it is now recognized that most genital infection due to HPV is subclinical and only identified with use of cytology, colposcopy, biopsy, and HPV DNA detection, the true extent of HPV is vastly underestimated by use of data related to clinically apparent genital warts (8). Koutsky et al. (64) reported that among the 24 million persons in the United States estimated to be infected with HPV (based on techniques available in the late 1980s), approximately 1% had genital warts, 2% had subclinical HPV infection diagnosed by colposcopy, and 7% had HPV infection detected by DNA hybridization (64).

More recently, Koutsky and Kiviat (8) summarized the point prevalence of genital HPV infection detected by PCR methods among various populations of women with cytologically normal Papanicolaou smear results. The HPV prevalence in these cytologically healthy women ranged from 1.5% to 44.3% (sexually active young

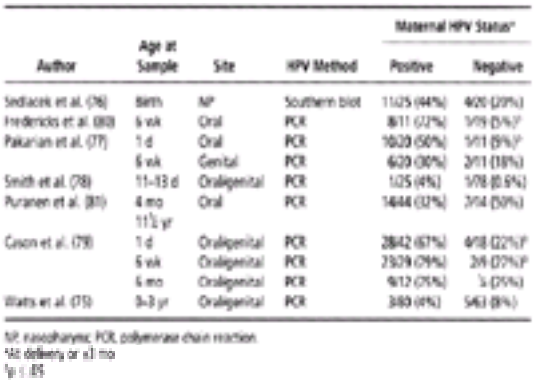
women), with a weighted average of HPV prevalence among 12,595 cytologically healthy women being 16.2%. Recently, serologic assays for specific HPV types based on conformationally correct antigen targets in the form of virus-like particles have been developed. Seroprevalence studies using this technology have demonstrated that in women without evidence of clinically apparent HPV infection, 3% to 43% have antibodies to HPV-16 and 9% to 25% have antibodies to HPV-6 or HPV-11 (65,66,67,68,69 and 70). Koutsky and Kiviat (8) suggested, based on current data, that more than 50% of sexually active adults in the United States have been infected with one or more genital HPV, with most HPV infections subclinical, unrecognized, and benign (8).

Genital HPV infections are primarily transmitted through sexual contact, and the sexual transmission of HPV associated with genital warts (condyloma acuminatum) is well established (8). The lesions occur in the urogenital and anorectal areas. Young, sexually active adolescents and adults are the highest prevalence group for genital warts. Koutsky et al. (64) estimated that 1% of sexually active men and women between 18 and 49 years of age have external genital warts. Oriel (10) described an infectivity rate of about 65% among sexual contacts. Sand et al. (71) more recently reported a similar rate in a study of 90 male partners of women with genital warts, of whom 62 (69%) were found to have histologically confirmed genital warts. The average incubation period is 2 to 3 months. Women are affected with a frequency equal to that of men.

Laryngeal (respiratory) papillomatosis in infants and children is caused by HPV-6 and HPV-11. The route of transmission for laryngeal papillomatosis is not completely understood (72). Potential routes include transplacental, intrapartum in the birth canal, or postnatal. Whereas infection of the maternal genital tract with HPV is common, juvenile-onset recurrent laryngeal papillomatosis is rare (73,74). Thus, only a small proportion of children born to infected mothers develop respiratory papillomas. It is estimated that the risk of HPV transmission from infected mother to neonate ranges from 1 per 100 to 1 per 1,000 exposures (73,74 and 75). Several reports suggest that HPV infection may be transmitted *in utero.* Shah et al. (73) reported a case of laryngeal papillomatosis developing in the first year of life in a child delivered by elective cesarean section in the presence of intact membranes. Recurrent laryngeal papillomatosis has a bimodal age distribution, which includes juvenile-onset recurrent respiratory papillomatosis (JO-RRP) and adult-onset recurrent respiratory papillomatosis (AO-RRP) (74). Approximately one half of cases are JO-RRP, with symptoms commencing shortly after birth, during infancy, or preschool age. In AO-RRP, the peak incidence is during the third and fourth decades of life (74). The juvenile form of the disease, particularly during the first several years of life, tends to be more severe and is characterized by rapid regrowth and the need for frequent, repeated surgical excisions. The traditional view has been that JO-RRP predominantly occurs in the first-born child of a young (adolescent) pregnant woman who delivers vaginally (74,75).

Studies assessing the risk for and incidence of transmission of HPV from mother to infant have produced conflicting data (Table 7.27). Initial studies with PCR-based methods for detection of HPV DNA revealed rates of detection of HPV in the first 24 to 48 hours of life, ranging from 4% to 72% among infants born to mothers with genital HPV detected during pregnancy, compared with 0.6% to 20% among infants born to women without HPV detected during pregnancy (76,77,78 and 79). Similarly, studies performed at 6 weeks of life demonstrated variable rates of detection

(77,79,80). In addition, the rates of detection of HPV were not always significantly different between infants born to HPV-positive mothers and those born to HPV-negative mothers (77,79,80).



Author	Age at Sample	Site	HPV Method	Maternal HPV Status* Positive	Negative
Sedlacek et al. (76)	Birth	NP	Southern blot	11/25 (44%)	4/20 (20%)
Fredericks et al. (80)	6 wk	Oral	PCR	8/11 (72%)	1/19 (5%)†
Pakarian et al. (77)	1 d	Oral	PCR	10/20 (50%)	1/11 (9%)†
	6 wk	Genital	PCR	6/20 (30%)	2/11 (18%)
Smith et al. (78)	11–13 d	Oralgenital	PCR	1/25 (4%)	1/78 (0.6%)
Puranen et al. (81)	4 mo	Oral	PCR	14/44 (32%)	3/14 (50%)
	11½ yr				
Cason et al. (79)	1 d	Oralgenital	PCR	28/42 (67%)	4/18 (22%)†
	6 wk	Oralgenital	PCR	23/29 (79%)	2/8 (27%)†
	6 mo	Oralgenital	PCR	9/12 (75%)	1/4 (25%)
Watts et al. (75)	0–3 yr	Oralgenital	PCR	3/80 (4%)	5/63 (8%)

NP, nasopharynx; PCR, polymerase chain reaction.
*At delivery or ≤1 mo
†$p \leq .05$

TABLE 7.27. DETECTION OF HUMAN PAPILLOMAVIRUS (HPV) DNA IN ASYMPTOMATIC CHILDREN

More recent studies have continued to produce inconsistent results. Puranen et al. (81) reported that HPV DNA was found in the nasopharyngeal aspirate in 39 of 106 infants (37%) born to mothers with no clinical signs of HPV infection. In 29 mother-infant pairs, the mother and infant samples were positive for the same type of HPV, and the overall concordance between HPV types in mother and her newborn was 69% (81). Five infants born by cesarean section were positive for the same HPV type as their mother, suggesting possible transplacental exposure or ascending HPV despite intact membranes. Tseng et al. (82) studied 301 pregnant women (vaginal delivery, 160; and cesarean section, 141) and their neonates for the presence of HPV-16 and HPV-18 (82). The frequency of HPV-16/18 was 22.6% (27 of 68), and at birth, they noted an overall transmission rate of 39.7% (27 of 68). A significantly higher rate of HPV-16/18 infection was detected by birth among infants delivered vaginally (18 of 35, or 51.4%) versus those delivered by cesarean (9 of 33, or 27.3%) ($p = 0.042$). Although these results demonstrate that neonates delivered vaginally are at higher risk for exposure to HPV, delivery by cesarean section is also associated with substantial risk (82). Both these studies (81,82) were single-point evaluations and do not establish whether HPV DNA detected at birth necessarily causes a persistent infection with HPV or whether it reflects contamination with maternal DNA. On the other hand, Watts et al. (75) in a prospective cohort study reported that the risk for any given women-infant pair appears to be small. These authors followed 151 pregnant women who had livebirths and were evaluated at less than 20 weeks and between 34 and 36 weeks of gestation for HPV by clinical, colposcopic, and PCR means. Their infants were evaluated at birth, 6 weeks, and 6, 12, 18, 24, and 36 months of age for HPV DNA on samples from mouth, external genitalia, and anus. During pregnancy, 112 (74%) of 151 women had evidence of HPV. Among the infants, HPV was detected in only three (4%) of 80 infants born to women with HPV present at 34 to 36 weeks of gestation and from 5 (8%) of 63 born to women without HPV DNA (75). The upper 95% confidence interval (CI) of perinatal transmission from women with HPV was only 2.8% (75). Similarly, Tenti et

al. (83) reported that pregnant women with latent HPV infections have a low potential of transmitting the virus to the oropharyngeal mucosa of their newborns. This study included 711 mother-infant pairs, with 73 (5.2%) of the mother's HPV-infant pairs and 37 (5.2%) of the mothers being HPV positive (by PCR). HPV DNA was detected in 11 neonates born vaginally to HPV-positive women, yielding a vertical transmission rate of 30% (95% CI, 15.9–47.0). These authors noted that the time between rupture of the membranes and delivery seemed to be a critical factor in predicting transmission (83). With rupture of the membranes for less than 2 hours, all 11 infants were negative for HPV, although with rupture of the membranes for 2 to 4 hours and more than 4 hours, the rate of HPV positivity was 7 of 21 (33%) and 4 of 5 (80%), respectively (p = 0.001) (83). By 5 weeks after birth, all infants tested negative and remained so throughout the 18-month follow-up, suggesting the HPV-positive infants at birth were contaminated but not infected.

Many studies have demonstrated that high-risk HPV types (particularly 16 and 18) may also be transmitted from mother to infant (75,81,82,83 and 84). Whether such transmission plays a role in the etiology of cervical dysplasia and malignancy in later life is unknown (84). In addition to duration of membrane rupture and vaginal route of delivery, viral load of HPV is shown to correlate with transmission from HPV-infected mothers to infants (85). oreover, the onset of clinical respiratory papillomatosis is highly variable, with only 25% of cases presenting within 1 year of delivery, and by 3 years of age, only 50% of cases had their onset (86). This later finding suggests the possibility of postnatal transmission as a route of infection.

In adults, transmission of HPV is overwhelmingly by sexual contact (8). The infected partner may have clinical or subclinical disease. Risk factors associated with HPV infection include increasing numbers of sex partners (8,87), cigarette smoking (87), and long-term use of oral contraceptives (87).

Nonsexual transmission of HPV also appears to occur (8,88,89,90,91 and 92). Recent studies noted that anogenital warts in children occurred as a result of hand warts in the child or relatives (88,89). In addition, Fairley et al. (90) reported that many cases of anogenital warts in children are caused by HPV types 1 to 4, which are commonly found on the hands. Lastly, Sonnex et al. (91) have demonstrated that HPV DNA of the genital types can be detected on the fingers of some men and women with genital HPV infection. This latter study may explain the findings of Morrazzo et al. (93) in their study of women who were sexually active with women. These authors reported that HPV DNA was detected in 30% of the 149 women (93). Even among the 21 subjects reporting no prior sex with men, HPV DNA was detected in 19% and SILs in 14% (93). As summarized by Mindel and Tideman (92), although transmission of genital HPV by fingers may occur occasionally, most infections occur as the result of genital-to-genital contact. Similarly, although fomites (gloves, surgical instruments, and underwear) have been demonstrated to carry HPV DNA, transmission of HPV by these routes is a rare occurrence (94).

Immunosuppressive states are associated with a higher frequency of genital warts. An increase has been reported in women who have received renal transplants (95), and the frequency and severity of genital warts are increased during pregnancy (96,97). HPV infection in HIV-infected women has been the focus of recent interest. Of most concern has been the finding that neoplastic lesions of the cervix associated with genital HPV infection progress at an increased rate in HIV-infected women (98). A comprehensive discussion of HPV infection in HIV-infected women can be found in

Chapter 10 (Acquired Immunodeficiency Syndrome [AIDS]).

Clinical Presentation

Infections with HPV present with a wide variety of clinical findings (11,99). The spectrum of HPV disease includes (a) clinically evident disease with genital warts, (b) subclinical (latent) HPV infection of the cervix, vagina, vulva, perineum, or anus, (c) intraepithelial neoplasia of the cervix, vulva, vagina, penis, and anus, and (d) respiratory (laryngeal) papillomatosis (11,99).

Whereas genital HPV infections are most commonly transmitted through direct skin-to-skin contact with infectious lesions, it is believed that HPV transmission also occurs in the absence of lesions during the latent phase of disease (99,100). The incubation time for HPV disease ranges from 1 month to 2 years (99). Clinical manifestations (e.g., genital warts) occur on average 2 to 4 months after reported exposure to HPV infection. However, most HPV infections remain subclinical or latent and may progress to clinical disease, persist as subclinical disease, or resolve (94,100).

Recently, as summarized by Beutner et al. (56), the American Medical Association (AMA) Expert Panel on External Gential Warts developed a consensus statement regarding the diagnosis, treatment, and evaluation of patients with external genital warts. External genital warts are defined as visible warts occurring in the urogenital or anorectal regions (56). The morphologic appearance of external genital warts is similar whether they involve the penis, urethra, perineum, anus, rectum, vulva, or vagina. Lesions on the cervix may be flat and endophytic (101). External genital warts are frequently multifocal, presenting with one or more lesions at a single anatomic site (e.g., vulva) (56,102). Alternatively, they may be multicentric, presenting with lesions on different anatomic sites (56,102).

The AMA consensus group delineated four morphologic types of external genital warts: condylomata acuminata, which are cauliflower shaped; papular warts, which are dome shaped (usually skin colored) 1- to 4-mm papules; keratotic genital warts, which have a thick horny layer and may resemble a common wart or seborrheic keratosis; and flat-topped papules, which appear macular to slightly raised (56). These morphologic types are usually associated with one of the two major types of skin found in the genital area (56). Condylomata acuminata occur generally on moist, partially keratinized and non–hair-bearing skin. Keratotic and smooth, papular external genital warts occur on fully keratinized skin (hair bearing or non–hair bearing). Flat-topped papular warts occur on either type of skin surface.

In heterosexual men, the penis is the most common site for genital warts. Perianal and intraanal condylomata occur in patients who engage in anal intercourse (homosexual men or heterosexual women). Genital warts in women are generally located on the external genitalia and perineal regions. Exophytic genital warts (condylomata acuminata) usually present initially at the fourchette and adjacent labia and then may spread rapidly to involve other parts of the vulva (103). Oriel (104) estimates that in 20% of cases, condylomata also appear on the perineum and perianal area. The vagina may also be affected, rarely extensively. In addition, the cervix may be involved but with “flat condylomata,” rather than the typical exophytic lesions. Cervical lesions that occur are flat and endophytic condylomata and can usually only be recognized with the aid of a colposcope (101). In fact, a high

proportion of cervical lesions previously classified as cervical intraepithelial neoplasia (CIN) grade 1 or 2 are now considered to be this variant of genital HPV infection. The colposcopic findings of HPV infection of the cervix have been well described (104). In general, after treating the cervix with 5% acetic acid, the transformation zone contains areas that are white, often with a raised and roughened surface. Subclinical HPV infection of the vulva has also been described (103). It presents as “microwarts” or flat vulvar lesions visible with colposcopy after application of acetic acid. Walker et al. (105) have demonstrated that about 50% of women with vulvar warts have concomitant evidence of cervical HPV infection.

Overwhelming patients with genital warts present complaining of lesions on their genitalia and rarely report other symptoms (8). On occasion, patients present with itching, burning, pain, or bleeding (8). Although women with genital warts often complain of vaginal discharge, such symptoms are felt to be primarily due to coexisting vaginal infections or other STDs and not HPV (8,106).

Persons with impaired cell-mediated immunity due to HIV infection, immunosuppressive therapy, lymphomas, or pregnancy may present with extremely large genital warts (8). Such genital warts referred to as “giant condylomata” or Loewenstein-Burschke tumors (107). These lesions rarely can become locally invasive and destructive, but they do not metastasize and usually contain HPV-6 DNA.

Meisels et al. (101) initially reported that grossly normal cervical epithelium may show cytologic or histologic evidence of HPV infection. Indeed, these subclinical manifestations of HPV infection are now recognized as the most common HPV lesions in the cervix and vagina (33). It is now appreciated that subclinical HPV infection also frequently involves the vulva, anus, and penis.

Diagnosis

Koutsky and Kiviat (8) have emphasized the importance of diagnosing two clinical manifestations of genital HPV infections: (a) genital warts that can be visualized with the naked eye and (b) SILs of the cervix detected by routine cytologic screening.

Most condylomata are so characteristic in appearance that the diagnosis is primarily made on visual examination alone. External genital warts usually can be easily visualized with gross inspection, and such clinical diagnosis has been demonstrated to be very accurate and consistent with histologic diagnosis (108). Some experts suggest that use of a bright light and a hand lens, a magnifying loop, or colposcopy may be useful in identifying external genital warts. In women, lesions that must be differentiated from genital condylomata include epithelial papillae, small sebaceous glands, and perianal fibroepithelial polyps. The most important lesions that must be differentiated from genital warts are the condylomata lata of secondary syphilis. If lesions appear atypical or the diagnosis is uncertain, biopsy should be performed. Additional indications for biopsy include (a) progression of disease during treatment, (b) prompt or frequent recurrences, and (c) warts are pigmented, indurated, ulcerated, or fixed to underlying tissue (108). Patients with external genital warts should be screened for other STDs (57,58). Histologically, condylomata acuminata are characterized by papillated epidermal hyperplasia, parakeratosis, koilocytes, occasional nontypical mitotic figures, and increased numbers of dilated and tortuous capillaries. This is particularly true among sexually active patients younger than 25

years and should include testing for chlamydia, gonorrhea, syphilis, HIV, hepatitis B, and vaginitis (56).

Subclinical HPV infection is generally diagnosed with colposcopy. In women, these lesions involve the cervix, vagina, vulva, and anus, whereas in men, the penis is the most common site. After the application of 3% to 5% acetic acid, subclinical HPV infection has a shiny white color with irregular borders and satellite lesions. The lesions of HPV infection are not confined to the transformation zone of the cervix, as are the lesions of CIN. Two characteristic colposcopic findings for subclinical HPV infection of the vagina have been described. These are aspirates that are multiple short, pointed spikes (109) and those that exhibit reverse punctuation, which is a diffuse pattern of slightly raised white dots (111). For vulvar subclinical HPV lesions, the colposcopy characteristics are not well delineated, and biopsy may be required to make the diagnosis. Use of the acetowhitening is not routinely recommend as a screening test for subclinical HPV infection of the external genitalia (108). This test is not highly specific and has a low positive predictive value in many populations (56,108).

Additional diagnostic modalities for subclinical HPV infections of the female genital tract have been used. Cytology of exfoliated cells is noninvasive and fairly inexpensive. The most characteristic cytologic finding of HPV infection is koilocytosis; dyskaryosis, atypical basal cells, and multinucleation have also been described. Cytology has excellent specificity, but only fair sensitivity. Histologic findings in genital warts include basal cell hyperplasia, acanthosis, papillomatosis, koilocytosis, parakeratosis, and mild nuclear atypia. The koilocyte is the most specific histologic marker for HPV infection, except for HPV types 16 and 18 where koilocytes are often absent (31). Increasingly, DNA hybridization techniques have been used to demonstrate HPV in tissue. HPV DNA has been demonstrated in clinical genital warts (condyloma acuminatum) (31), subclinical genital HPV infections (31), lesions of CIN (111,112 and 113), and invasive genital cancers (114). Because certain types of HPV (i.e., 16 and 18) are associated with cervical carcinoma, HPV typing may become an important clinical tool. For now, it is primarily a research technique. In particular, detection and typing of HPV have no proven benefit in the diagnosis and management of external genital warts (56).

In the diagnosis of HPV infection, it is critical to distinguish well-developed disease patterns from low-grade, potentially nonspecific changes (115). Well-developed changes in the cervix include (a) low-grade SILs such as exophytic condylomata acuminata, flat condylomata, and CIN1; (b) high-grade SILs—CIN1 and CIN2; and (c) invasive cervical cancer. On the vulva, well-developed lesions include exophytic condylomata, bowenoid dysplasia, and a small portion of squamous vulvar cancers. This differentiation serves as the basis for determining appropriate management and avoiding unnecessary overaggressive therapy for low-risk HPV infection.

Because genital warts frequently present with more than a single lesion on one genital site and with lesions on multiple sites, it is important that the entire lower genital tract be examined (8). Thus, speculum examination to detect vaginal and cervical warts is recommended for women with external genital warts.

Although many clinical epidemiologic studies over the past decade have provided strong evidence for the role of specific HPV types in the pathogenesis of squamous cell carcinoma of the genital tract, testing for specific HPV types in the management

of women with abnormal Papanicolaou smears remains to be of proven usefulness (8,16,72,116). Although tests that detect several types of HPV DNA or RNA in cells scraped from the cervix are available, the CDC notes that the clinical use of such tests in the management of patients is unclear (72). Furthermore, the CDC suggests that management decisions should not be made on the basis of HPV typing and that screening for subclinical genital HPV infection using DNA or RNA tests or acetic acid is not recommended. Kaufman et al. (116) evaluated the use of HPV detection in identifying women with abnormal Papanicolaou smear results who can be safely followed up with cytologic study only (116). These authors concluded that HPV screening did not appear to be valuable in identifying those women with abnormal Papanicolaou smear results who can be followed up only with cytologic study (116). Among the 486 women with low-grade SIL on Papanicolaou smear, 35.4% had high-risk HPV DNA detected, and in the 592 women with high-grade SIL, only 44.4% had high-risk HPV DNA detected (116). Moreover, only 38.7% of biopsy specimens with CIN and 56.2% with CIN2 or CIN3 had high-risk HPV DNA. Thus, the sensitivity of HPV DNA detection to identify biopsy-confirmed CIN2 or CIN3 was 55.7% and the positive predictive value of the test was only 34.9% (116).

Recently, studies using the second-generation HPV test, Hybrid Capture II HPV DNA Assay (Digene Corp) have demonstrated improved sensitivities when used as a primary screening test (117,118,119,120 and 121). Schiffman et al. (120) compared HPV testing using the hybrid capture technique with HPV testing using conventional cytology, liquid-based cytology, computer-assisted cytology, and cervicography. Using a 1-pg/mL level for HPV positivity, these authors reported a sensitivity for detecting high-grade SILs or cancer of 88.4%, compared with 77.7% for conventional cytology. However, the reported specificity of 89% was lower than that for cytology (94.2%) and the positive predictive value in their population (prevalence for high-grade SIL and cancer, 1.6%) was 11.6%, compared with a positive predictive value of 18% for cytology. Wright et al. (121) reported on an unscreened population near Cape Town, South Africa, in which high-grade SIL or cancer was detected in 4.25% of women. These authors compared self-collected vaginal swabs, clinician-obtained conical brush samples for HPV testing, conventional cytology, cervicography, and visual inspection after application of 5% acetic acid. Using second-generation HPV testing and the l-pg/mL cutpoint resulted in a sensitivity of 83.9% for clinician-obtained samples and 66.1% for self-collected samples (121). The sensitivity of self-collected samples was similar to that of cytology (66.1% vs. 67.9%, respectively, for atypical squamous cells of undetermined significance [ASCUS]) (121). Although these studies by Schiffman et al. (120) and Wright et al. (121) demonstrate that screening with HPV testing can potentially enhance the sensitivity of cervical cancer screening, whether such testing is feasible, affordable, or will result in fewer cases of invasive cervical cancer requires further study (122).

Treatment

The therapeutic approach for HPV infection of the genital tract is dependent on the anatomic location of the disease (external genitalia/perianal, cervical, vaginal or urethral), the clinical presentation of the disease (clinical vs. subclinical), and the extent of the disease. In addition, it is important to acknowledge that no therapy has been shown to eradicate HPV (72). Thus, unlike bacterial STDs in which eradication is possible, the primary goal of treatment of external genital warts (condyloma acuminatum) is to eliminate warts that cause physical or psychologic symptoms or distress (72,108). Treatment of genital warts is frustrating for patients and providers

(123). In addition, treatment is often painful, expensive, and ineffective, with frequent recurrences (72). Treatment can be classified as either patient applied or health care provider administered. Table 7.28 summarizes the efficacy and recurrence rates of therapeutic methods for genital warts from randomized, clinical trials. Overall, these treatment studies have demonstrated that currently available therapeutic methods are 22% to 94% effective in clearing exophytic genital warts and that recurrence rates are usually at least 25% within 3 months (72,98). In placebo-controlled studies, genital warts have resolved spontaneously in 20% to 30% of patients within 3 months (98). Elimination of genital warts may or may not decrease infectivity because internal sites (vagina or cervix) and clinically normal skin may act as reservoirs for infection (56,72).

Therapy	Efficacy	Recurrence Rate	Relative Cost
Podofilox (124–142)	45–88%	0–60%	+
Imiquimod (143–145)	37–85%	13–19%	++
Podophyllin (146–150)	22–79%	11–74%	+
Trichloracetic acid (98)	81%	36%	++
Cryotherapy (151,152)	63–88%	21–39%	++
Electrodesiccation (98,153)	55–94%	11–22%	+++
Excision (98,152)	89–93%	29%	+++
Intralesional interferon (146,154,155)	36–62%	0–33%	++++
Systemic interferon (146,153,156,157)	11–23%	9–36%	++++
Laser surgery (158,159)	23–40%	95%	+++++

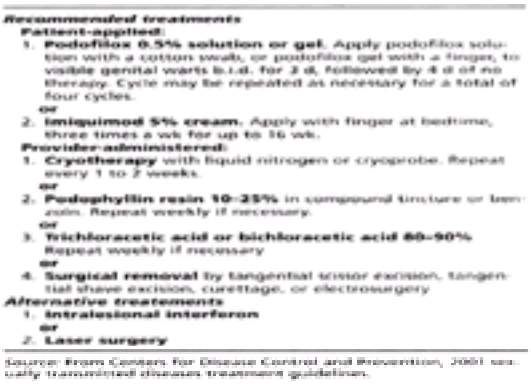
Note: Data from randomized clinical trials.

TABLE 7.28. EFFICACY AND RECURRENCE RATES FOR TREATMENT OF GENITAL WARTS

Recently, the CDC issued new recommendations for the treatment of HPV infection (72). As noted earlier, the CDC concurs that the primary goal in the treatment of visible genital warts is the removal of symptomatic warts (72). In most patients, treatment will induce wart-free periods of varying lengths. The CDC notes that there is no evidence indicating that currently available treatment modalities eradicate or affect the natural history of HPV infection (72). Visible genital warts that are not treated may resolve spontaneously, remain unchanged, or increase in size or number. Furthermore, there is no evidence that treatment of external genital warts affects the development of cervical cancer (72).

For external genital/perianal warts (condyloma acuminatum), the recommended therapeutic measures are listed in Table 7.29. The CDC suggests that treatment of genital warts should be guided by patient preference, available resources, and health care provider experience (72). The CDC emphasizes that none of the currently available treatments is superior to other treatments and that no single treatment is ideal for all patients or all warts (72). Available treatments for visible genital warts are divided into two categories: (a) patient-applied therapies (e.g., podofilox and imiquimod) and (b) provider-administered treatments (e.g., cryotherapy, podophyllin resin, trichloracetic acid [TCA], bichloracetic acid [BCA], interferon, and surgery). Factors influencing choice of treatment include wart size, wart number, anatomic site, wart morphology, patient preference, cost of treatment, convenience, side

effects, and provider experience (72). Many patients require a course of therapy, rather than a single treatment, so providers must have a treatment plan or protocol for the management of genital warts (72). In this vein, the CDC recommends that the treatment modality should be changed if the patient has not improved substantially after three provider-administered treatments or if the warts have not completely cleared after six treatments (72). For patient-applied treatment, it is not advisable to exceed the manufacturer's recommendation for duration of therapy (56).



Recommended treatments

Patient-applied:

1. **Podofilox 0.5% solution or gel.** Apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts b.i.d. for 3 d, followed by 4 d of no therapy. Cycle may be repeated as necessary for a total of four cycles.

   or

2. **Imiquimod 5% cream.** Apply with finger at bedtime, three times a wk for up to 16 wk.

Provider-administered:

1. **Cryotherapy** with liquid nitrogen or cryoprobe. Repeat every 1 to 2 weeks.

   or

2. **Podophyllin resin 10–25%** in compound tincture of benzoin. Repeat weekly if necessary.

   or

3. **Trichloracetic acid or bichloracetic acid 80–90%** Repeat weekly if necessary

   or

4. **Surgical removal** by tangential scissor excision, tangential shave excision, curettage, or electrosurgery

Alternative treatments

1. **Intralesional interferon**

   or

2. **Laser surgery**

Source: From Centers for Disease Control and Prevention, 2001 sexually transmitted diseases treatment guidelines.

TABLE 7.29. TREATMENT OF EXTERNAL GENITAL WARTS: 2001 CENTERS FOR DISEASE CONTROL RECOMMENDATIONS

Complications rarely occur if the treatments available for genital warts are properly used (56,72). With ablative procedures, scarring in the form of hypopigmentation or hyperpigmentation is common (72). Although depressed or hypertropic scars are rare, they can occur when there has been insufficient time for healing between treatments (72). On rare occasions, disabling chronic pain syndromes such as vulvodynia or hyperesthesia of the treatment site will occur (72).

Podofilox (Condylox) 0.5% topical solution or gel is available for patient-applied treatment of external genital warts (condyloma acuminatum). Podofilox has been demonstrated to be safe and effective for self-treatment of genital warts (124). Podofilox is the most biologically active component found in podophyllin. In contradistinction to podophyllin, podofilox is a pure standardized compound, does not contain the mutagens quercetin and kaempherol, is stable with a long shelf life, does not require that it be washed off after application, and is associated with little risk for systemic toxicity (125,126). Podofilox is an antimitotic drug that results in destruction of warts (72). Efficacy in recent clinical trials for complete clearance of warts ranged from 45% to 88% and recurrence occurred within 3 months in 33% to 60% of patients (125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141 and 142). Local irritation such as burning and pain appears to be more frequent with podofilox but is generally mild and without systemic toxicity. The major advantage offered by podofilox over alternative therapies for genital warts is that it can be self-applied by patients. Thus, although the drug cost of podofilox is greater than that of podophyllin, the overall cost is significantly less because fewer physician office visits are required (124). The CDC suggests that, if possible, the health care provider should apply the

initial treatment to demonstrate the proper application technique and to identify which warts should be treated (72). Other advantages of podofilox are relatively low cost, simple to use, and no systemic toxicity. The safety of podofilox in pregnancy has not been established, so its use in pregnancy is contraindicated. In addition, podofilox is not approved for perianal, rectal, urethral, or vaginal condylomata acuminata. The total wart area treated should not exceed 10 cm^2, and a total volume of podofilox should not exceed 0.5 mL per day (72).

Imiquimod (Aldara) is another patient-applied topical therapy for external genital warts. Imiquimod is a nonnucleoside heterocyclic amine, immune response–enhancing agent (143,144). The proposed mechanism of action for imiquimod is stimulation (induction) of the production of interferon, interleukin-6, and tumor necrosis factor-4 (72,143,144,160,161). Clinical studies have demonstrated the 5% cream preparation of imiquimod is twice as effective as the 1% cream (108). Among patients treated with imiquimod 5% cream, between 37% and 19% had recurrences during the follow-up period (143,144 and 145). Minimal systemic absorption of imiquimod occurs through intact skin (160). Generally, imiquimod 5% cream is well tolerated. The most common application-site reactions include itching, burning, pain, and soreness (160). Before wart resolution, local inflammatory reactions are common but are usually mild to moderate (72). These local skin reactions include erythema, erosion, excoriation/flaking, edema, ulceration, and induration at the wart site (160). It is recommended that the treatment area be washed with mild soap and water 6 to 10 hours after the application (72). The safety of imiquimod during pregnancy has not been established, so imiquimod is contraindicated in pregnancy (72).

Cryotherapy has a demonstrated efficacy of 63% to 88%, with a recurrence rate of 21% to 39% (98). Advantages of cryotherapy include low cost, no requirement for anesthesia, and lack of scarring when performed appropriately. However, it does require special equipment and is associated with moderate pain during and after the procedure.

Podophyllin therapy had been the traditional nonsurgical approach to external genital warts in women. The use of 10% to 25% podophyllin has resulted in initial clearance of genital warts in 22% to 77%, with recurrences noted in 11% to 74% (98). Among randomized trials, the results were 32% to 79% and 27% to 65% for efficacy and recurrences, respectively (148,149,152,155). Podophyllin therapy is simple to use, relatively inexpensive, and relatively safe when used for external condyloma acuminata (98). However, application must be by a health care provider, which requires office visits and results in increased costs. A small amount of podophyllin resin in compound tincture of benzoin should be applied to each wart and allowed to air dry before allowing the patient to assume a normal sitting or standing position (72,108). As noted by the CDC, overapplication or failure to air dry can result in local irritation secondary to spread of the agent to adjacent areas (72). Beutner et al. (108) suggest that when podophyllin is properly applied, there is no need to protect surrounding skin with petrolatum or other barriers. Moreover, they question the routine advice to wash the treated area 1 to 4 hours after the application (108). Podophyllin has strong antimitotic activity and may be teratogenic. Although the active agent, podophyllin resin, is not a mutagen, the suspension does contain carcinogens including the flavenoids, quercetins, and kaempherol (108). Side effects associated with the use of podophyllin include skin ulceration, erythema, irritation, pain, burning, and soreness (108). During pregnancy, lesions may be profuse and

vascular, which predisposes for systemic absorption of podophyllin. Podophyllin is contraindicated in pregnancy (72) because absorption may be harmful to the mother and fetus. Cases have been reported in which fetal death and maternal neuropathy have occurred with the use of podophyllin in pregnant women (162).

TCA and BCA are caustic agents that destroy warts by chemical coagulation of the proteins (108,163,164 and 165). Although TCA and BCA are widely used, they have been rarely studied and scant data are available on the inefficacy. The few published studies have demonstrated clearance rates of between 50% and 100% and recurrence rates of between 6% and 50% (163,164 and 165). TCA is easily applied, modest in cost, and safe. TCA requires office visits for application by a health care provider. TCA solutions have a low viscosity and can spread rapidly to damage adjacent tissue (72). Thus, it is recommended that TCA and BCA be applied sparingly and allowed to dry before the patient sits or stands (72). If pain is severe, the acid can be neutralized with talc or baking soda (72). Skin ulcerations, erosions, erythema, irritation, pain, burning, and soreness are adverse side effects with the use of TCA or BCA (108). These agents are not contraindicated during pregnancy and TCA use in pregnancy has not been associated with adverse effects (162).

Surgical removal of external genital warts can be accomplished by physically destroying the lesions with curettage or electrosurgery or tangentially excising the warts with scissors or scalpel (72,108). The major advantage of surgical removal is that it renders the patient wart free usually in a single visit (72,108). On the other hand, surgical excision requires significant clinical training and experience, additional equipment, and a longer office visit (72,108). Moreover, surgical excision requires local anesthesia.

Few data are available concerning the efficacy of electrodesiccation. Two randomized trials noted by the CDC demonstrated an efficacy of 35% to 94%, with recurrence rates of 11% to 22% (98). The cost of electrodesiccation is moderate, local anesthesia is required, and discomfort is moderate. No additional hemostasis is required. Potential scarring is a risk. Whereas electrocautery disrupts warts and coagulates proteins of treated tissues, curettage and scissors or scalpel excision directly remove genital warts (109). Most warts are exophytic and excision can be accomplished with a resulting wound that only extends into the upper dermis (72). Hemostasis will need to be accomplished with cautery or a chemical styptic and suturing should not be required (73). The CDC notes that surgery is most beneficial for those patients with either a large number or a large area of genital warts (72). Reported studies of surgical excision demonstrate nearly complete eradication within 1 to 6 weeks of treatment and recurrence rates of between 8% and 35% within 1 year of treatment (108). The only contraindication to surgical excision is a known bleeding abnormality (108).

The use of podophyllin, podofilox, and imiquimod are contraindicated in pregnancy. During pregnancy, the best approach to treatment is removal of lesions by excision, electrocautery, or cryosurgery. TCA application has been used in pregnancy without adverse effects (162). Laser therapy is another alternative among pregnant women with extensive disease.

Alternative therapies for external genital warts include intralesional interferon and laser therapy (72). The use of the antiviral agent interferon for the treatment of external genital warts, particularly difficult to treat, persistent, or resistant lesions, has

received considerable attention. Systemic interferon either alone or as an adjuvant to other therapies for the treatment of external genital warts has proved to be disappointing and is not recommended (72). Intralesional interferon appears to be more useful and the efficacy and recurrence rates of this approach are comparable to those of other treatment modalities (72). Published studies of intralesional interferon (as both primary and adjunctive therapy) have demonstrated that 42% to 62% of patients have complete clearance of their warts within 12 to 20 weeks of injection and that recurrent lesions occur in 19% to 53% of patients (usually 20% to 30% recurrence rates) (147,154,156,166,167,168,169,170 and 171). However, interferon therapy is not recommended for routine use because of high cost, inconvenient routes of administration, frequent office visits, and high frequency of systemic adverse effects (72). These include a flulike syndrome (headache, chills, fevers, and myalgias), impaired concentration, nausea and vomiting, fatigue and malaise, dizziness, back pain and dyspepsia, leukocytopenia, thrombocytopenia, and an elevated aspartate aminotransferase level (108). Local reactions include injection site pain, burning, itching, irritation, and rarely local bleeding (108).

Laser therapy has also been disappointing when evaluated in randomized, clinical trials. Reid et al. (158) reported complete clearance of vulvar warts or vulvar intraepithelial neoplasia in only 8 (40%) of 20 women. Peterson et al. (159) noted complete clearance in only 5 (23%) of 22 patients with multiple warts. Moreover, laser is expensive, painful, requires anesthesia, and carries a significant risk for scarring.

Two treatments for external genital warts are currently under investigation. 5-Fluorouracil-epinephrine-bovine-collagen gel implant is injected directly below the wart (108). This agent combines the antimetabolite 5-fluorouracil with a drug delivery system composed of the vasoconstrictor epinephrine and a biodegradable stabilizing gel (bovine collagen). Cidofovir is an acyclic nucleoside phosphate analog with broad-spectrum antiviral activity against DNA viruses (108).

For the treatment of vaginal exophytic warts, the recommendations include (a) cryotherapy with liquid nitrogen, (b) 80% to 90% TCA or BCA, or (c) 10% to 25% podophyllin in compound tincture of benzoin (72). Because of concern with potential systemic absorptions, we prefer not to use podophyllin in the vagina. If one elects to use podophyllin, the treatment area must be dry before removing the speculum. Podophyllin is contraindicated in pregnancy. Podofilox is not approved for vaginal use because the patient cannot visualize the lesions for application. For urethral meatus warts, either cryotherapy with liquid nitrogen or podophyllin is recommended (72). With anal warts, cryotherapy with liquid nitrogen, 80% to 90% TCA or BCA, or surgical excision is recommended (72).

Subclinical genital HPV infection is more common than exophytic genital warts (72). The approach to the management of subclinical HPV infection is based on an understanding of several key points (72). HPV infection is often indirectly diagnosed on the cervix by Papanicolaou smear, colposcopy, or biopsy. A definitive diagnosis of HPV infection requires detection of viral DNA or RNA or capsid proteins. There is poor correlation between Papanicolaou smear diagnosis of HPV and detection of HPV DNA in cervical cells (98). Acetowhitening is not specific for HPV infection (72). HPV-induced cellular changes in the cervix are similar to those seen with mild dysplasia and often resolve spontaneously (72). The clinical applicability of the available tests for detection of various types of HPV DNA remains unresolved. Thus,

the CDC recommends that management decisions should not be made on the basis of HPV DNA test results. Whether identification of the presence of high-risk HPV types (e.g., 16 and 18) will influence management remains to be determined.

In the absence of coexistent dysplasia, the CDC recommends no treatment for subclinical genital HPV infection diagnosed by Papanicolaou smear, colposcopy, biopsy, acetic acid soaking, or detection of HPV DNA or RNA, or capsid antigen (72). To date, no therapy has been demonstrated to eradicate subclinical HPV infection. HPV has been demonstrated in adjacent tissue after laser therapy of HPV-associated cervical dysphasia and attempted eradication of subclinical HPV with extensive laser vaporization. With coexistent dysphasia, management is determined by the grade of dysplasia present.

The CDC does not recommend examination of sex partners of patients with genital warts or subclinical HPV infection (72). Their rationale is that most sex partners are probably already infected subclinically with HPV. In addition, no practical screening tests for subclinical HPV infection currently exist. The use of condoms probably reduces transmission to uninfected (e.g., new) partners (72). However, condoms will not prevent reactivation of “latent” HPV.

In general, the presence of condyloma acuminatum or subclinical HPV infection is not an indication for performing a cesarean section (72). As discussed earlier, although HPV infection is common in women of reproductive age, laryngeal papillomas are rare, with an estimated transmission risk of 1 per 1,000 infected mothers (87). Clearly *in utero* transmission in the presence of intact membranes occurs, as does postnatal acquisition. However, with large condylomata, mechanical obstruction, and the risk of significant bleeding, a cesarean section may be necessary (72).

TRICHOMONIASIS

Trichomonas vaginalis is one of the most prevalent parasites in humans and is transmitted primarily via sexual intercourse. In the United States, *T. vaginalis* is found in about 10% of healthy women to nearly 50% in patients attending STD clinics. It has been estimated that more than 165 million infections per year occur worldwide, with approximately 5 million in the United States (1). For discussion of the epidemiology, clinical findings, diagnosis, and treatment of *T. vaginalis* infection, see the detailed discussion of trichomoniasis in Chapter 12 (Infectious Vulvovaginitis).

HEPATITIS B AND HEPATITIS C

Hepatitis B virus (HBV) is the causative agent for hepatitis B (formerly serum hepatitis). This agent may be acquired through sexual transmission, contaminated blood and blood products, or perinatal transmission. Hepatitis C virus (HCV) is the causative agent for hepatitis C (formerly non-A, non-B hepatitis). It also is transmitted sexually and perinatally, in addition to by contaminated blood. The role of HBV and HCV in maternal infection and its effect on the fetus and neonate are detailed in Chapter 16 (Perinatal Infections). Discussion of the epidemiology, clinical presentation, diagnosis, and treatment of HBV and HCV infection can be found in Chapter 9 (Hepatitis Infection).

GENITAL MYCOPLASMATA

The clinically significant genital tract mycoplasmata include *Mycoplasma hominis, Ureaplasma urealyticum* (formerly T-mycoplasma), and *M. genitalium.* The clinical manifestations, diagnostic features, and management of *Mycoplasma* infections are described in Chapter 4 (Genital Mycoplasmas).

CHLAMYDIA TRACHOMATIS

C. trachomatis has emerged as one of the most common sexually transmitted organisms. Chlamydia is discussed in detail in Chapter 5 (Chlamydial Infections), and its role in STDs will be only briefly reviewed in this section.

C. trachomatis has been implicated in an expanded spectrum of diseases. Chlamydia is the major etiologic agent for nongonococcal urethritis, postgonococcal urethritis, and epididymitis in young men. Among women, *C. trachomatis* has been associated with mucopurulent endocervicitis, endometritis, PID, infertility due to tubal factors, and the acute urethral syndrome. In pregnant women, vertical transmission resulting in chlamydial conjunctivitis or pneumonia is well documented. A role for *C. trachomatis* in postpartum infections, premature labor and delivery, rupture of the membranes, and perinatal mortality has also been demonstrated but is more controversial.

The epidemiology, clinical presentation, diagnosis, and treatment of chlamydial infection are described in Chapter 5 (Chlamydial Infections) and will not be discussed here.

HERPES SIMPLEX VIRUS

Genital herpes is an STD caused by HSV types 1 and 2 (HSV-1 and HSV-2). HSV is associated with chronic recurrent genital tract disease and severe neonatal infection. Herpes is discussed in detail in Chapter 8 (Mixed Anaerobic-Aerobic Infection and Pelvic Abscess).

CYTOMEGALOVIRUS

CMV is a member of the Herpesviridae family. It is a DNA virus that is capable of producing recurrent or latent infection. Initially, CMV was associated with fulminant neonatal infection characterized by jaundice, thrombocytopenia, purpura, hepatosplenomegaly, and CNS involvement. Subsequently, CMV has been recognized as a fairly common cause of subclinical congenital infection. More recently, CMV has been recovered from both semen and cervical secretions and has been implicated as a sexually transmitted agent. The impact of CMV as a perinatal infection and STD organism is discussed in Chapter 16 (Perinatal Infections).

HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus that is the etiologic agent for AIDS. HIV infection is pandemic, with

more than 500,000 cases of AIDS having been reported in the United States. The primary route of transmission of HIV has been sexual. Although in the United States and Europe, the predominant route has been homosexual contact, in Africa heterosexual spread has been the major transmission vehicle. An increasing role for transmission by needle sharing among intravenous drug abusers has been seen in the United States and western Europe. Recently, HIV infection in women has become an important aspect of the epidemic in the United States.

Of recent concern is the perinatal transmission of HIV from infected mothers to their offspring. In Chapter 10 (Acquired Immunodeficiency Syndrome [AIDS]), the epidemiology, biology, clinical manifestations, and perinatal effects of HIV infection are discussed in detail.

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8

MIXED ANAEROBIC-AEROBIC PELVIC INFECTION AND PELVIC ABSCESS

ANAEROBIC-AEROBIC INFECTION

The past several decades have produced significant advances in the understanding of the microbiology and pathogenesis of pelvic and intraabdominal infections. Considerable progress has also been made in the diagnosis and treatment of these infections. Despite these advances, infection remains a major source of morbidity and mortality on obstetric and gynecologic services. During this revolution in the biology of infectious diseases, various pathogens emerged, in succession, which were of concern for obstetrician-gynecologists (3,4). Initially, obstetrician-gynecologists focused on Gram-positive organisms such as the group A b-hemolytic streptococcus, which was the primary cause in the preantibiotic era of maternal mortality. The 1950s saw the emergence of *Staphylococcus aureus,* and with it came the first major concern over antibiotic resistance. In the 1960s, the emphasis was on Gram-negative Enterobacteriaceae, particularly *Escherichia coli* and the Gram-positive rod *Clostridium perfringens.* Beginning in the 1970s, the importance of anaerobic bacteria, particularly Gram-negative anaerobic rods such as *Bacteroides fragilis,* became apparent. In the 1980s, the role of *Prevotella bivia* and *Prevotella disiens* (formerly *Bacteroides bivius* and *Bacteroides disiens,* respectively), the most important anaerobes in obstetric and gynecologic infections, was described (8). Investigations in the late 1970s and early 1980s have demonstrated the importance of mixed anaerobic and facultative bacteria in the pathogenesis of pelvic infections (1,2,3 and 4,8,9,10,11,12 and 13). Also during this time, the group B streptococcus emerged as a major pathogen in neonatal sepsis and maternal infectious morbidity (14). Clinicians recognized the importance of *Chlamydia trachomatis* in pelvic infection (15,16) during the 1980s. In the late 1980s and early 1990s, some investigators have suggested an increasing importance of the enterococcus in pelvic and intraabdominal infections (17,18 and 19). Fortunately, *Pseudomonas aeruginosa* remains an uncommon pathogen in obstetric and gynecologic patients, and in general, the emergence of methicillin-resistant *S. aureus* and multidrug-resistant enterococci has not affected obstetric and gynecologic

services.

Etiology And Pathogenesis

To prevent significant morbidity or potential mortality, the obstetrician-gynecologist must develop appropriate management plans for the treatment of soft tissue pelvic infections. These plans must be based on knowledge of the microorganisms involved, the microbiologic techniques capable of isolating the mixed anaerobic and facultative bacteria present, and the available antibiotics and their spectrum of activity, and they must be based on the awareness of the potential side effects of these antibiotics and the realization that surgical intervention may be necessary to eradicate the infection. Furthermore, because mixed infections with multiple species of aerobic and anaerobic bacteria involve a complex flora that precludes rapid identification of the pathogens involved in these infections, therapy of most pelvic infections must be empiric (20).

Two basic underlying principles are crucial to an understanding of the pathogenesis of female genital tract infections. The first of these is that except for a few microorganisms such as the group A b-hemolytic streptococcus, *Neisseria gonorrhoeae,* and *C. trachomatis,* the pathogens that cause upper genital tract infections in the pelvis arise from the normal microflora of the vagina and cervix. The lower genital tract of healthy women is a complex ecosystem that harbors multiple bacterial species—anaerobic, aerobic, and facultative bacteria. This complex microflora is discussed in Chapter 1 (Clinical Microbiology of the Female Genital Tract) and is only briefly summarized here. An average of six to seven organisms reside in the vagina and cervix and are present in concentrations of 10^8 to 10^9 bacteria per milliliter (21). In this milieu, anaerobes are the most prevalent organisms and outnumber the facultative bacteria by a factor of 10 : 1. The anaerobic bacteria commonly identified in the normal microflora of the vagina and cervix include lactobacilli; anaerobic Gram-positive cocci (peptostreptococci); and *Prevotella* sp (formerly *Bacteroides* sp). *P. bivia* and *P. disiens* have been identified as the major components of the anaerobic vaginal flora. Thus, *P. bivia* and *P. disiens* appear to be the unique anaerobes for the female genital tract, analogous to the role of *B. fragilis* as the predominant anaerobe in the colon and rectum. The most common facultative bacteria of the normal vagina and cervix appear to be lactobacilli, streptococci, *Staphylococcus epidermidis,* and *Gardnerella vaginalis. E. coli* is recovered in 5% to 30% of healthy female lower genital tracts; other Enterobacteriaceae are generally found in less than 10% of the population. *Lactobacillus* sp, as discussed in Chapter 1 (Clinical Microbiology of the Female Genital Tract), are the predominant organisms of the normal vaginal flora. In particular, lactobacilli, which produce hydrogen peroxide, play a key role in maintaining the normal vaginal ecology (22).

The second guiding principle is the recognition that Pasteur and Koch's theorem that a single pathogen is responsible for a single infection no longer holds (23). Rather, identification of the presence in pelvic infections of a complex microflora, which includes multiple aerobic and anaerobic bacteria, has led to the so-called polymicrobic etiology of infection. In general, anaerobic bacteria are recovered from nearly two thirds of pelvic infections and are the only isolates in approximately one third of such infections (Table 8.1). It has become apparent that anaerobic bacteria are probable pathogens in virtually all types of bacterial infections of the female pelvis (11,15,24,25,26,27,28,29,30,31,32,33,34,35,36 and 37) (Table 8.2). Whereas

initially the literature emphasized anaerobic Gram-positive cocci and clostridia, subsequent investigations documented the important role of anaerobic Gram-negative bacteria in pelvic infections, particularly *B. fragilis.* The recovery rate for *B. fragilis* in these studies ranged from 0% to 79% (9,11,13,15,25,26,27,28,29,30,31,32 and 33,38,39,40,41,42,43,44 and 45). Although these investigations demonstrated that *B. fragilis* was both a frequent and major pathogen in soft tissue pelvic infections, more recent studies have shown that unlike intraabdominal infections in which *B. fragilis* has remained the anaerobe most commonly isolated (1,2,5,6), this organism is not the most frequent anaerobe identified in pelvic soft tissue infections (15,42,44,45). Although *B. fragilis* is generally recovered from less than 5% of pelvic infections, in current studies when present, it is still associated with significant infectious morbidity (7). Recent studies have shown the importance of *P. bivia* and *P. disiens,* which have been recovered from pelvic infections in 19% to 44% and 2% to 16% of patients, respectively (8,13,15,30,33).

Study	Infection	No. of Cases	Anaerobes Recovered (%)
Altemeier, 1940 (24)	TOA	25	22 (88)
Rotheram and Schick, 1969 (25)	Septic abortion	76	48 (63)
Swenson et al., 1973 (26)	Various	24	21 (87)
Thadepalli et al., 1971 (27)	Abscess	16	16 (100)
Chow et al., 1975 (28)	PID	21	10 (48)
Goide et al., 1977 (29)	TOA	37	32 (87)
Sweet and Ledger, 1979 (31)	Various	125	75 (60)
Gall et al., 1981 (30)	Various	43	37 (86)
Cunningham et al., 1981 (31)	Various	100	71 (71)
Cunningham et al., 1982 (32)	Post-cesarean section	136	98 (72)
Gibbs et al., 1983 (33)	Post-cesarean section	113	79 (70)
Sweet et al., 1983 (16)	PID	74	68 (92)
Sweet et al., 1984 (34)	Various	60	54 (90)

PID, pelvic inflammatory disease; TOA, tuboovarian abscess.

TABLE 8.1. PREVALENCE OF ANAEROBIC ORGANISMS IN PELVIC INFECTIONS

Endomyometritis (Pregnant)	Skene and abscess
Parametritis	Endometritis (nonpregnant)
Pelvic cellulitis	Acute pelvic inflammatory disease
Pelvic abscess	Pyosalpinx
Septic pelvic thrombophlebitis	Tuboovarian abscess
Pelvic peritonitis	Intraamniotic infection
Bacteremia	Abscess of adjacent tissue
Wound infection	Groin, perirectal, abdominal wall
Necrotizing fasciitis	Bacterial vaginosis
Bartholin gland abscess	Septic abortion

TABLE 8.2. PELVIC INFECTIONS IN WHICH ANAEROBIC BACTERIA ARE COMMONLY ECOVERED

Although anaerobic bacteria are recovered in a high percentage of genital tract infections and only anaerobic bacteria may often be isolated, most of these infections are mixed with facultative and/or aerobic organisms. Thus, the term “mixed anaerobic-aerobic infections” is often applied to soft tissue infections of the upper female genital tract.

Alterations in the normal environment resulting from medical therapy or operative intervention can result in conditions appropriate for selective anaerobic survival and proliferation (3). Basically, such conditions are provided by a lowering of the oxidation-reduction potential of tissue. Various factors facilitate the access of the normal microflora of the cervix and vagina to the upper genital tract and allow the appropriate environmental conditions for the organisms to act as pathogens producing clinical infection. These factors include damage to mucosal surfaces, impairment of local vascular supply, presence of traumatized or necrotic tissue, the presence of foreign bodies, and the growth of exogenous organisms that produce tissue destruction. Surgical procedures result in breaks in mucosal surfaces, which allows bacteria from the vagina and the cervix to gain access to usually sterile tissues. The blood supply to the distal ends of surgical pedicles is interrupted, and when such pedicles have been exposed to the bacteria of the lower genital tract during a surgical procedure (e.g., vaginal hysterectomy), a nidus for infection may be established. Such avascular necrotic tissue is an ideal environment for the growth and multiplication of anaerobic bacteria. Foreign bodies have long been recognized as a nidus for infections, such as septic abortions. More recently, it has been appreciated that suture material in the skin and subcutaneous tissue of abdominal wounds may serve as a nidus for infection. Intrauterine contraceptive devices (IUDs) are foreign bodies that predispose to the development of pelvic infections involving the uterus, fallopian tubes, and ovaries by facilitating ascent of microorganisms, interference with local defense mechanisms, and the breakdown of mucosal surfaces.

Traumatized necrotic tissue may be present after a long, neglected labor or surgical procedure. A prime example of the importance of tissue destruction in the pathogenesis of infection is cesarean section. In this procedure, necrotic uterine musculature results from the surgical incision and closure of this incision with suture. The necrotic tissue is exposed to the vaginal and cervical bacteria that have gained access to the amniotic fluid as a result of labor, ruptured membranes, and multiple vaginal examinations during labor. It should not be surprising, therefore, that women undergoing cesarean section have a significantly greater risk of endomyometritis than those delivering vaginally (3).

The initial growth of exogenous microorganisms such as *N. gonorrhoeae* or *C. trachomatis* in acute salpingitis causes tissue destruction and alteration of the local environment, which may pave the way for lower genital tract flora, particularly anaerobes, to gain access to the upper genital tract. However, in most instances, the anaerobic and aerobic bacteria gain access to the upper genital tract without antecedent primary infection by an exogenous organism. Several recent investigations have demonstrated that bacterial vaginosis, an alteration of the vaginal flora characterized by increased frequency and concentration of anaerobic bacteria, is associated with the development of acute pelvic inflammatory disease (PID) (46,47,48,49 and 50).

Thus, most female genital tract infections are polymicrobic and are mixtures of anaerobic and facultative bacteria. Table 8.3 is a schematic depiction of the common pathogenic organisms involved in female genital tract infections. Of the facultative or aerobic organisms, the most common Gram-positive organisms are streptococci, including hemolytic and nonhemolytic species, and *S. epidermidis*. The major clinical streptococci based on the Lancefield classification are groups A, B, and D. This identification is important in selecting antimicrobial therapy. Although many streptococci are exquisitely susceptible to penicillin G, those in group D, and particularly the enterococci, are notable exceptions. Of the staphylococci, *S. epidermidis* is most commonly recovered from sites of pelvic infection; the pathogenicity of this organism in pelvic sepsis is controversial, but it has been recognized to be a pathogen, particularly in the presence of a foreign body. *S. aureus,* although not as common, is a recognized pathogen in occasional pelvic infections.

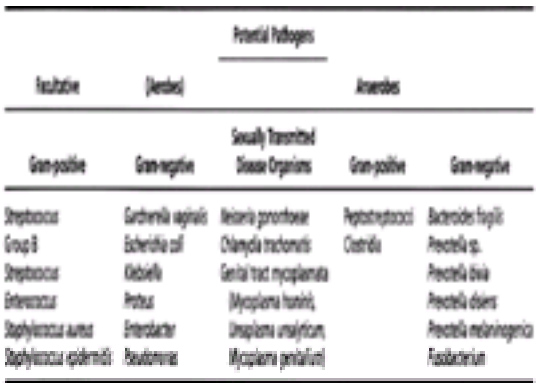

TABLE 8.3. SCHEMATIC DEPICTION OF THE MAJOR PATHOGENS IN THE ETIOLOGY OF FEMALE GENITAL TRACT INFECTIONS

Of the Gram-negative facultative organisms, *E. coli* is by far the most common. *Klebsiella, Proteus,* and *Enterobacter* organisms are much less frequent; *Pseudomonas* organisms are extremely rare in nonimmunosuppressed obstetric and gynecologic patients as a source of soft tissue infection. *G. vaginalis* is a major component of the normal vaginal flora, being isolated in 50% to 60% of healthy women. It is recognized as a putative agent in synergy with anaerobic bacteria in bacterial vaginosis. More recently, *G. vaginalis* has been recovered from the upper genital tract (uterus or fallopian tube) of patients with PID or endomyometritis. Increasingly, *G. vaginalis* has been noted to be the most common Gram-negative facultative bacteria recovered from soft tissue pelvic infections. *N. gonorrhoeae* is a Gram-negative diplococcus. It is an exogenous sexually transmitted organism that is a frequent pathogen in PID. *C. trachomatis,* an obligatory intracellular bacterium, is now recognized with increasing frequency as a major pathogen in PID (15). The role of *C. trachomatis* as a putative agent in postpartum endomyometritis has been suggested (51) but is not definitely established. The role of the genital tract mycoplasmata as primary pathogens remains controversial except for being present

in the milieu of bacterial vaginosis.

Of the Gram-positive anaerobic organisms, the peptostreptococci are the most common. At present, clostridia are infrequently recovered from obstetric and gynecologic infections. As discussed in Chapter 1 (Clinical Microbiology of the Female Genital Tract), the genus *Bacteroides* has been recently redefined, with the genus *Bacteroides* now restricted to organisms previously considered the *B. fragilis* group (*Bacteroides caccae, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides eggerthii, Bacteroides merdae, Bacteroides stercoris, Bacteroides vulgatus,* and *Bacteroides uniformis*); *B. fragilis* is the type species of the genus (52). Of the Gram-negative anaerobes, *P. bivia* and *P. disiens* are the most common. Various other *Prevotella* sp are involved in pelvic infections. *B. fragilis,* although less frequent, is still a major cause of morbidity and serious infection on obstetric and gynecologic services. The virulence of *B. fragilis,* despite its lower incidence of occurrence, probably accounts for the attention this organism has received. *Fusobacterium* organisms are also very common.

Microbiologic Techniques for Isolation of Pathogens from Pelvic Infections

Because soft tissue upper genital tract infections are caused to a large extent by pathogens that are derived from the normal endogenous flora of the vagina and cervix and these infections often include anaerobic bacteria, special culture methodology must be employed to prevent contamination by the normal microflora and to ensure isolation and recovery of anaerobic bacteria. The common obstetric and gynecologic infections are listed in Table 8.4, and the appropriate site from which to obtain cultures in these particular infections is noted. In addition, the microorganisms that are cultured from the site of infection are listed. The specifics as to the anaerobic technology and methods of recovery for *N. gonorrhoeae, C. trachomatis,* and *Mycoplasma* sp are described in detail in Chapter 2 (Use of the Microbiology Laboratory in Infectious Diseases).

Type of Infection	Sites for Cultures	Microorganisms
Endomyometritis/endometritis	Endometrial aspiration	Anaerobes/facultatives Neisseria gonorrhoeae Chlamydia trachomatis
Pelvic inflammatory disease	Endocervical	N. gonorrhoeae C. trachomatis
	Culdocentesis, Endometrial aspirate, Laparoscopy	N. gonorrhoeae Anaerobes/facultatives C. trachomatis
Pelvic abscess	Aspiration of abscess Abscess wall obtained at surgery	Anaerobes/facultatives
Posthysterectomy Pelvic cellulitis Cuff abscess	Culdocentesis Aspiration	 Anaerobes/facultatives Anaerobes/facultatives

TABLE 8.4. FEMALE PELVIC INFECTIONS: MICROBIOLOGIC EVALUATION

Controversy has existed over the issue of obtaining cultures before institution of empiric antibiotic therapy for soft tissue pelvic infections. Concerns over cost, inappropriate laboratory technology to identify organisms (particularly anaerobic

bacteria) in polymicrobic infections, and excellent clinical response to empiric therapy in most instances (more than 80%) have resulted in many clinicians omitting the pretherapy culture. On the other hand, only by obtaining pretherapy cultures can the microorganisms and their susceptibility patterns be identified, thus providing the database required for empiric therapy. Moreover, in few patients who do not respond to empiric therapy, the pretherapy culture results will allow altering the treatment regimen based on data, rather than a probability choice. Lastly, the increasing resistance of many bacteria to various antimicrobials, often geographically based, strengthens the argument for obtaining cultures. Even when dealing with anaerobic bacteria, the traditional approach of relying on antimicrobial susceptibility data from large research centers no longer is sufficient (7,53,54,55,56,57,58 and 59). As noted by Turgeon et al. (58), the heterogeneity of species' isolation and the differences in resistance rates of these species demonstrate the need to identify important clinical isolates to guide empiric therapy of infections caused by these organisms. Furthermore, they suggested that because of the changing susceptibility patterns over time and the variability in resistance rates among hospitals, there is a need for periodic antimicrobial susceptibility testing of each medical center by a referral center (58).

In patients with endomyometritis after either cesarean section, vaginal delivery, or abortion, the appropriate site for obtaining specimens is the endometrial cavity, not the cervix or lochia. We use endometrial biopsy aspiration techniques to obtain these specimens. As described in detail in Chapter 14 (Pelvic Inflammatory Disease), microbiologic specimens for PID may be obtained from several sites. From the cervix, it is appropriate to culture only for *N. gonorrhoeae* and *C. trachomatis.* Recently, antigen-detection methods (monoclonal fluorescent antibody staining or immunoassay) and polymerase chain reaction and ligase chain reaction techniques have become available for detecting *C. trachomatis.* The ideal specimen site is the fallopian tube, obtained via laparoscopy, but this is not universally applicable. Currently, an endometrial aspirate is our preference for obtaining specimens from patients with PID. In patients with pelvic abscesses, it is almost useless to obtain a culture from the lower genital tract. Instead, the appropriate specimen is from the abscess itself. At the time of surgical management of abscesses, both an aspirate from the purulent material and most importantly, a piece of the abscess wall should be sent to the laboratory for processing. Alternatively, the use of percutaneous aspiration of abscesses under sonographic direction can provide an ideal specimen for anaerobic and aerobic bacteria. Lastly, it is crucial to recognize that posthysterectomy pelvic infections do not occur in the vagina. Thus, vaginal cultures are an inappropriate method to obtain isolates. If pelvic cellulitis has developed postoperatively, the infection is in the peritoneal cavity, and the appropriate specimen is peritoneal fluid, obtained via culdocentesis. For a postoperative cuff abscess, aspiration of the purulent material from the apex of the vagina is acceptable. These specimens should be processed for anaerobic and facultative bacteria.

Management of Pelvic Infections

Selection of antimicrobial agents for the treatment of pelvic infections is based on knowledge of the microorganisms usually involved, the nature and severity of the infection, and the susceptibility patterns of available antimicrobial agents. In addition, cost of treatment must be considered, but only when efficacy and safety are equivalent. It is now widely accepted that pelvic infections are characteristically due

to mixtures of anaerobic bacteria (particularly *Peptostreptococcus* sp, *B. fragilis* group, *Prevotella* sp, *P. bivia, P. disiens,* and *Prevotella melaninogenica*), facultative Gram-negative Enterobacteriaceae such as *E. coli,* and facultative streptococci. In patients with acute PID, *N. gonorrhoeae* and *C. trachomatis* are frequent pathogens with or without mixed anaerobic-aerobic bacteria.

In addition to recognizing the susceptibility patterns of the potential pathogens, one can consider several other useful factors when determining the initial selection of antimicrobial therapy for these mixed pelvic infections. It is crucial that the antimicrobial agent reach the infected space, such as an abscess, soft tissue spaces of the pelvis, or amniotic fluid. The efficacy of new antimicrobial agents can be assessed in experimental animal models. However, ultimately the efficacy of antibiotics must be compared in prospective randomized clinical trials.

Experimental models of intraabdominal sepsis have enhanced our knowledge of both the pathogenesis and the microbiology of these infections and their therapy. The intraabdominal sepsis model of Weinstein et al. (60) is an excellent description of the pathogenesis of mixed aerobic-anaerobic infections of the abdomen and pelvis (Fig. 8.1). The initial stage of peritonitis, sepsis, and an associated high mortality rate of approximately 40% appear to be due to Gram-negative facultative bacteria, particularly *E. coli.* The surviving animals over the several days after the initial stage progress into a secondary phase, characterized by the development of intraabdominal abscesses. The microorganisms associated with these abscesses are anaerobes, particularly *B. fragilis.* A similar biphasic disease process occurs in many clinical entities that are encountered in obstetrics and gynecology. Although PID, pelvic cellulitis, and endomyometritis are analogous to the initial phase of peritonitis in this model, these infections, if untreated or inadequately treated, will progress to an abscess stage characterized by the presence of entities such as pyosalpinx, tuboovarian abscess (TOA), or pelvic abscess. In this model, whereas *E. coli* by itself produced a high rate of mortality and *B. fragilis* (the encapsulated strain) by itself produced abscesses almost universally, the enterococcus, neither by itself nor in synergy with *E. coli* or *B. fragilis,* appeared to be a pathogen. Whether the enterococcus plays a major etiologic role in mixed anaerobic-aerobic infections of the pelvis is controversial. Initial experimental models suggested that the enterococcus plays only a minor role, relying on a synergistic relationship with anaerobes (60,61 and 62). More recent experimental models suggest that the enterococcus has a role in the pathogenesis of intraabdominal sepsis (63,64). Matlow et al. (63) demonstrated, in a model of mixed peritoneal infection, an increased incidence of intraabdominal abscesses and a higher mortality when *Enterococcus faecalis* was part of the inoculum. Similarly, Montravers et al. (64) reported that high concentrations of *E. faecalis* played an important role in the mechanisms of bacterial synergy in experimental peritonitis. These authors demonstrated that *E. faecalis* exerted a synergistic role in maintaining high titer levels of other pathogens in peritoneal exudates and in increasing the frequency of bacteremia with these strains (64). Brooks (65) has also demonstrated, in a model of soft tissue infection, a synergistic effect between *E. faecalis* and *B. fragilis.* Recent clinical investigations also suggest that the enterococcus may be a pathogen of importance in pelvic infections and an increasing problem, particularly in patients who have received prophylactic cephalosporins (17,19). Although the general consensus has been that enterococci are less important than other organisms in mixed infections in nonimmunocompromised patients (20), patients not responding to empiric regimens that do not provide coverage against the enterococcus are commonly provided

additional coverage that is effective against enterococci.

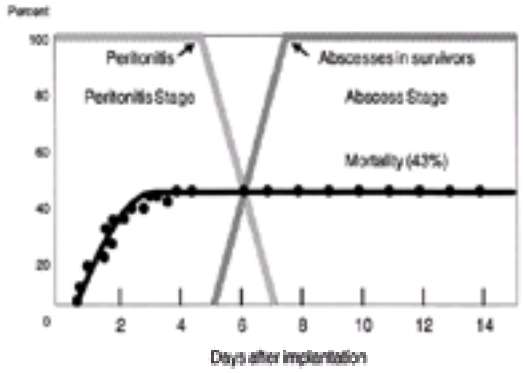

FIGURE 8.1. Biphasic disease model of intraabdominal and pelvic infections. Role of aerobes and anaerobes in the biphasic animal model.

The Weinstein animal model has also been used in an attempt to identify the appropriate management for mixed infections (61). Classically, physicians have been trained to apply a single antimicrobial agent to treat a monoetiologic agent in infection. With the recognition that we were dealing with multiple organisms, both aerobes and anaerobes, it became crucial to determine whether most of the organisms recovered from the site of infections must be treated, or whether only particular agents require therapy. In this animal model, it became apparent that although treatment of the peritonitis stage with agents effective against only the Gram-negative facultative bacteria such as *E. coli* would prevent the initial stage of peritonitis and sepsis, it had almost no effect on the subsequent development of abscesses (Table 8.5). On the other hand, with agents effective against only anaerobic bacteria, such as clindamycin or metronidazole, although the abscess stage was prevented, the animals universally developed peritonitis with a high mortality rate. It became apparent that either combination therapy with agents effective against both anaerobic bacteria and Gram-negative facultative bacteria or single agents effective against both components was necessary to prevent peritonitis, sepsis, and its associated high mortality, as well as the development of intraabdominal abscesses (61,62).

Treatment Regimen	Mortality Rate (%)	Abscess Formation (%)
Untreated controls	58/57 (37)	99/99 (100)
Cefazolin	2/30 (7)	14/28 (50)
Gentamicin	2/57 (4)	54/55 (98)
Clindamycin	21/60 (35)	2/39 (5)
Clindamycin plus gentamicin	5/58 (7)	3/53 (6)
Cefoxitin	0/30	2/30 (7)

Based on Weinstein WM, Onderdonk AB, Bartlett JG, Gorbach SL. Experimental intraabdominal abscesses in rats: development of an experimental model. Infect Immun 1974;10:1250–1255.

TABLE 8.5. EFFECT OF ANTIMICROBIAL TREATMENT ON THE MORTALITY RATES AND INCIDENCE OF ABSCESS FORMATION IN AN ANIMAL MODEL OF INTRAABDOMINAL SEPSIS

This basic tenet of using combination or single-agent therapy that is effective against the resistant Gram-negative anaerobes such as *B. fragilis, P. bivia,* and *P. disiens* early in the disease process has been demonstrated to be appropriate and applicable to the clinical situation as well. The investigation by diZerega et al. (66) was a bell weather study that clearly identified the benefits of this early aggressive approach in the therapy against resistant anaerobes. In a study involving post–cesarean section endometritis, these investigators were able to demonstrate that those patients who initially received an agent effective against *B. fragilis* (clindamycin) had significantly less morbidity, required less additional antibiotics or surgical intervention, had less serious infection-related complications such as abscesses or septic pelvic thrombophlebitis, and spent a mean of 1.6 fewer days in the hospital, compared with those women receiving an agent (penicillin) that did not cover the anaerobic Gram-negative rods of the *Bacteroides* (*Prevotella*) group (66). This study dramatically changed the approach to clinical management of soft tissue pelvic infections. Before this report, the traditional approach in obstetric and gynecologic infections had been to initiate treatment with ampicillin or a first-generation cephalosporin alone or in combination with gentamicin. Antianaerobic drugs such as clindamycin or chloramphenicol were reserved for patients not responding to initial therapy. After publication of these results, early aggressive initial treatment with a regimen including an agent effective against *Prevotella* sp and *B. fragilis* became the standard of care.

Table 8.6 is an attempt to simplify the approach to managing pelvic infections by organizing the pathogenic organisms into five major groups according to antimicrobial susceptibility patterns. The anaerobes, other than *B. fragilis, P. bivia,* or *P. disiens*—particularly peptostreptococci—are extremely common in pelvic infections. They are sensitive to multiple antibiotics, including penicillin, ampicillin, first-, second-, and third-generation cephalosporins, chloramphenicol, clindamycin, extended-spectrum penicillins such as piperacillin and mezlocillin, and the blactam agents combined with enzyme blockers such as Augmentin, Timentin, Unasyn, and Zosyn. Gram-negative Enterobacteriaceae, particularly *E. coli,* are also very common in pelvic infections. Increasingly, these organisms are resistant to ampicillin and the first-generation cephalosporins (e.g., cephalothin, cefazolin). In the past, they generally required aminoglycoside for excellent coverage. However, second- and third-generation cephalosporins and cephamycins (cefoxitin, cefotetan, and cefmetazole) also are very active against the Enterobacteriaceae. The carbapenem, imipenem-cilastatin, is also very effective against Gram-negative facultative bacteria. Somewhat less effective are the extended-spectrum penicillins, such as piperacillin and mezlocillin. The monobactam agent aztreonam also provides excellent coverage against the Gram-negative aerobes. The blactam agents, combined with enzyme blockers, provide good to excellent activity against Enterobacteriaceae such as *E. coli*; Augmentin, Timentin, and Zosyn provide excellent coverage and Unasyn good coverage. Fluoroquinolones such as ciprofloxacin and ofloxacin also provide

excellent coverage against Gram-negative facultative bacteria.

1. Anaerobes other than *Bacteroides fragilis, Prevotella bivia,* or *Prevotella disiens* (especially peptostreptococci)	Common
2. Gram-negative enterobacteriaceae (especially *Escherichia coli, Klebsiella, Proteus*)	Common
3. Enterococci (? primary pathogen)	10%
4. Facultative streptococci (nonenterococcal)	Common
5. *B. fragilis, P. bivia, P. disiens,* Prevotella melaninogenica	Common

TABLE 8.6. FREQUENCY OF BACTERIAL PATHOGENS RECOVERED FROM PELVIC INFECTIONS

The enterococcus is isolated from the site of pelvic infections in 5% to 10% of patients. The role of this organism in pelvic infections remains controversial. Although in the past the enterococcus was not (as a general rule) thought to be a primary pathogen (13,20,67), it has on occasion been recovered as the sole pathogen from an infection site of the upper genital tract. In most instances, this occurs in patients who have recently received broad-spectrum antibiotics or cephalosporin prophylaxis. Several studies have stressed that the enterococcus is an increasing problem (17,18 and 19). The enterococcus has a unique antimicrobial susceptibility pattern; ampicillin or a combination of penicillin plus aminoglycoside is most effective. Vancomycin is the drug of choice for penicillin-allergic patients. The new extended-spectrum penicillins such as piperacillin and mezlocillin are also effective against the enterococcus, as are the blactam plus enzyme blockers. Among the later agents, Timentin does not provide as good coverage as that of Augmentin, Unasyn, and Zosyn. The carbapenem, imipenem-cilastatin, also provides very good coverage against most enterococci.

The aerobic streptococci, such as group B streptococcus, are also common in pelvic infections. These organisms are sensitive to various penicillins, ampicillin, first- and second-generation cephalosporins, extended-spectrum penicillins, and clindamycin. However, the coverage against these organisms by third-generation cephalosporins is not equal to that of the first- and second-generation cephalosporins.

The fifth group is comprised of the resistant Gram-negative anaerobes, which include *B. fragilis, P. bivia, P. disiens,* and *P. melaninogenica.* These are very common organisms in pelvic infections and have patterns of susceptibility demonstrating resistance to penicillin, ampicillin, and first-generation cephalosporins (68,69). Two thirds of these *Prevotella* (formerly *Bacteroides*) organisms produce blactamase enzymes (70). Among the antimicrobial agents with excellent coverage against *B. fragilis* and the *Prevotella* sp are clindamycin, metronidazole, and chloramphenicol. Also, the cephamycins (cefoxitin, cefotetan, and cefmetazole) and blactam agents plus enzyme blockers (Augmentin, Timentin, Unasyn, and Zosyn) provide excellent

coverage for these anaerobes. Piperacillin, mezlocillin, and to a more variable extent, the third-generation cephalosporin ceftizoxime provide good coverage.

The *in vivo* activity of available antimicrobial agents against the Gram-negative facultative and aerobic bacteria commonly recovered from the site of pelvic infections is depicted in Table 8.7. For the *in vivo* activity of antimicrobial agents against Gram-positive facultative and aerobic bacteria that are frequent pathogens in obstetric and gynecologic soft tissue infections, see Table 8.8.

	Escherichia coli	*Klebsiella*	*Proteus*
Ampicillin	++	+	++++
First-generation cephalosporins (cefazolin)	++ to +++	+++	++
Gentamicin/tobramycin	++++	++++	++++
Cefamandole	++++	+++	++++
Cefoxitin, cefotetan, cefmetazole	+++	+++	++++
Imipenem/cilastatin	++++	++++	++++
Piperacillin/mezlocillin	+++	+++	++++
Third-generation cephalosporins	++++	++++	++++
Aztreonam	++++	++++	++++
β-Lactam agents plus enzyme blockers (Augmentin, Timentin, Unasyn, Zosyn)	++++[a]	++++	++++
Fluoroquinolones (ciprofloxacin, ofloxacin)	++++	++++	++++

[a]Unasyn is less active than other agents in this group.

TABLE 8.7. *IN VITRO* ACTIVITY OF ANTIMICROBIAL AGENTS AGAINST GRAM-NEGATIVE FACULTATIVE BACTERIA COMMONLY RECOVERED FROM PELVIC INFECTIONS

	Group B Streptococcus	Enterococcus	Staphylococcus aureus[a]
Penicillin G	++++	+[b]	+
Ampicillin	++++	++++	+
First-generation cephalosporins (cefazolin)	++++	0	+++
Cefamandole	++++	0	++
Cefoxitin, cefotetan, cefmetazole	++++	0	+
Imipenem/cilastatin	++++	+++	+++
Gentamicin/tobramycin	0	+[b]	++
Third generation cephalosporins	++ to +++	0	++
Aztreonam	0	0	0
β-Lactam agents plus enzyme blockers (Augmentin, Timentin, Unasyn, Zosyn)	++++	++++[c]	+++
Fluoroquinolones	0	0	0
Clindamycin	+++ to ++++	0	++ to +++
Metronidazole	0	0	0

[a]Non-methicillin-resistant strains of *Staphylococcus aureus*.
[b]Synergistic activity of ampicillin or penicillin G plus gentamicin = ++++.
[c]Timentin is less active.

TABLE 8.8. *IN VITRO* ACTIVITY OF ANTIMICROBIAL AGENTS AGAINST GRAM-POSITIVE FACULTATIVE BACTERIA COMMONLY RECOVERED FROM OBSTETRIC AND GYNECOLOGIC INFECTIONS

Table 8.9 summarizes susceptibility patterns of anaerobic bacteria recovered from pelvic infections. Penicillin G and ampicillin remain extremely effective antimicrobial agents against Gram-positive anaerobic cocci such as peptostreptococci. However,

these penicillins have little, if any, activity against resistant Gram-negative anaerobes such as *B. fragilis, P. bivia, P. disiens, P. melaninogenica,* or most other *Prevotella* organisms. The extended-spectrum penicillins such as piperacillin and mezlocillin, when used in large doses, do provide fairly good activity against the *B. fragilis* group and *Prevotella* sp. The first- and second-generation cephalosporins, much like the penicillins, are very effective against anaerobic organisms other than the *B. fragilis* group, *Prevotella* sp, *P. bivia, P. disiens,* and *P. melaninogenica.* Of the second-generation cephalosporins, cefamandole still lacks adequate coverage against the *B. fragilis* group, *P. bivia, P. disiens,* and *P. melaninogenica.* On the other hand, the cephamycins (cefoxitin, cefotetan, and cefmetazole) provide excellent coverage against these organisms. Eighty-five percent to 95% of *B. fragilis* organisms are sensitive to cefoxitin, and upward of 95% of *P. bivia, P. disiens,* and *P. melaninogenica* are susceptible to easily obtained levels of cefoxitin. Development of resistance to cefoxitin by the *B. fragilis* group was demonstrated in some medical centers (20,68,69). However, the rapidly changing pattern of susceptibilities is appreciated with the more recent reports on *B. fragilis* susceptibilities by Cuchural et al. (54,55), which show that the resistance of the *B. fragilis* group to cefoxitin had significantly decreased from 12% in 1982 to 5% in 1986 and 1988. Moreover, Turgeon et al. (58) reported that only 2.9% of *B. fragilis* strains and 17.2% of non–*B. fragilis* strains are resistant to cefoxitin. The non–*B. fragilis* strains of the *B. fragilis* group are not frequent pathogens in pelvic infections. Most recently, Snydman et al. (59), in a multicenter study of *in vivo* susceptibility of the *B. fragilis* group in 1995 and 1996, reported that the rate of cefoxitin resistance to *B. fragilis* was 4.15% and to non–*B. fragilis* organisms 8.5%. Cefotetan has antimicrobial activity that is very similar to that of cefoxitin. However, *in vivo* testing has demonstrated a twofold to threefold tube dilution increase in the minimum inhibitory concentration (MIC) for cefotetan versus cefoxitin against the *B. fragilis* group (particularly non–*B. fragilis* strains), *P. bivia,* and *P. disiens.* The clinical significance of these *in vivo* differences is unclear (70), and clinical trials have demonstrated excellent results with cefotetan for the treatment of obstetric and gynecologic infections (45,71). Of concern is the recent multicenter analysis by Snydman et al. (59) demonstrating resistance rates to cefotetan of 19.2% and 63.5% for *B. fragilis* and the non–*B. fragilis* organisms, respectively. Clindamycin, chloramphenicol, and metronidazole have excellent activity against anaerobic bacteria, including the Gram-positive cocci, clostridia, *B. fragilis* group, *Prevotella* sp, *P. bivia, P. disiens,* and *P. melaninogenica.* Although all three are very effective against anaerobic bacteria, each has a drawback that the clinician must recognize. Clindamycin is associated with pseudomembranous colitis, as described in Chapter 23 (Antimicrobial Agents). Fortunately, this is a rare occurrence. Chloramphenicol has been reported to result in aplastic anemia in approximately 1 per 100,000 patients receiving the drug. Again, this is a rare occurrence but is often fatal when it does occur. With metronidazole, significant short-term side effects are relatively rare, but gastrointestinal tract intolerance is common. Although its theoretic carcinogenic potential is a drawback, concern over this complication has not been proven valid. All three of these agents have been demonstrated *in vivo* to be very effective against anaerobic bacteria, and prospective clinical studies have confirmed their clinical efficacy. However, *in vivo* studies during the past 15 years have demonstrated increasing resistance among the *B. fragilis* group to clindamycin (53,54,55 and 56,58). In general, 5% to 15% of *B. fragilis* organisms are resistant to clindamycin. The prevalence of clindamycin-resistant *B. fragilis* has increased steadily from less than 8% in the 1980s (53,54) to as high as 20% to 38% in some medical centers (72,73 and 74). In their recent survey of susceptibility to the *B. fragilis,* Snydman et al. (59) demonstrated resistance rates to clindamycin for 10.9% of *B. fragilis* isolates and 16.5% of the non–*B. fragilis* isolates.

However, clindamycin activity against members of the *Prevotella* sp has remained excellent. No large-scale resistance to metronidazole or chloramphenicol has emerged (53,54,55,56,57,58 and 59). Imipenem-cilastatin (Primaxin) has maintained excellent coverage against all clinically important anaerobes associated with pelvic infections and has demonstrated excellent clinical results (59,75,76 and 77). This is true of the blactam agents plus enzyme blockers as well (55,59).

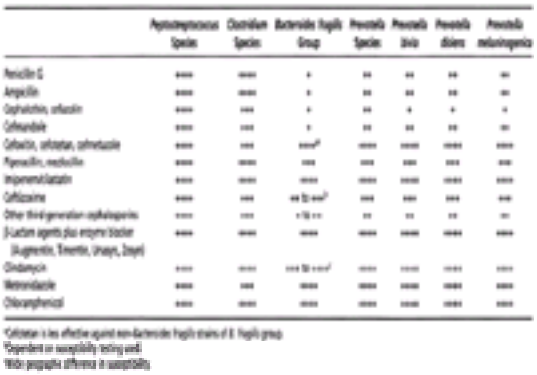

TABLE 8.9. *IN VITRO* ACTIVITY OF ANTIMICROBIAL AGENTS AGAINST ANAEROBIC BACTERIA COMMONLY RECOVERED FROM PELVIC INFECTIONS

A multitude of third-generation cephalosporins were developed, tested, and introduced into clinical medicine during the 1980s. These third-generation cephalosporins are discussed in detail in Chapter 23 (Antimicrobial Agents). The most controversial aspect of these third-generation cephalosporins has been the extent of their anaerobic coverage. Table 8.9 provides a comparison of the anaerobic spectrum of these agents.

In general, the third-generation cephalosporins have been shown to have their best activity against the Gram-negative Enterobacteriaceae, particularly *E. coli, Klebsiella,* and *Proteus* organisms. However, they have not demonstrated consistent activity against *P. aeruginosa.* These antimicrobial agents have reasonable activity against the facultative streptococci, but are less effective against *S. aureus* than the first-generation cephalosporins. Ceftizoxime has demonstrated a large degree of variability in its activity against anaerobes (20,78,79). The *in vivo* activity of ceftizoxime varies with the conditions of the susceptibility testing (78). Five percent (81) to 57% (20) of *B. fragilis* cases have been reported to be resistant to ceftizoxime. Snydman et al. (59) recently reported, in a multicenter survey, that 21.7% of *B. fragilis* and 20% of non–*B. fragilis* isolates were resistant to ceftizoxime. Limited clinical experience in the treatment of pelvic and intraabdominal infections has been good (80,81). With the exception of moxalactam, which had excellent anaerobic activity but is no longer available, the remaining third-generation cephalosporins provide poor activity against *B. fragilis* group, *P. bivia, P. disiens,* and *P. melaninogenica.*

Because of their frequency in pelvic infections, clinicians should assume that one of

these Gram-negative anaerobic rods is present whenever an infection of the female upper genital tract occurs and their choice of an antimicrobial regimen should include coverage for these resistant b-lactamase–producing anaerobes.

In evaluating the therapeutic response of obstetric and gynecologic infections, one must consider several factors: Not only is the patient's initial response to antimicrobial therapy crucial, but we must also evaluate the need for additional antimicrobial agents, the need for use of anticoagulants for the treatment of septic pelvic thrombophlebitis, and most importantly, the need for surgical intervention for either drainage or surgical extirpation of abscesses or infected tissues.

It is critical to keep in mind that early treatment, particularly against these Gram-negative–resistant anaerobic bacilli, plays a crucial role in resolving pelvic infections and in preventing severe morbidity and mortality due to infection in obstetric and gynecologic patients (10,13,66,67). Both animal model work (61,62) and clinical studies (66) have demonstrated the need for early aggressive antimicrobial therapy in the management of mixed aerobic-anaerobic infections, which includes antibiotics effective against the Gram-negative anaerobic bacilli, particularly *B. fragilis* group, *Prevotella* sp, *P. bivia, P. disiens,* and *P. melaninogenica.*

A schematic approach to the therapy of mixed aerobic-anaerobic pelvic infections is depicted in Fig. 8.2. The traditional approach to the management of these infections was the use of a penicillin-aminoglycoside regimen, ampicillin by itself, or a first-generation cephalosporin by itself. With such antimicrobial regimens, cure rates were obtained in 70% to 90% of patients. Those patients not responding within an appropriate period were then treated with clindamycin or chloramphenicol for supposed *B. fragilis* infection. Once again, the vast majority of patients would respond, but there consistently remained a small number of failures, of which 1% to 2% had pelvic abscesses requiring surgical drainage and 1% to 2% developed septic pelvic thrombophlebitis requiring anticoagulation therapy with heparin. More recently, a more aggressive approach has been used in which therapy is commenced at the level of agents effective against *B. fragilis* and the *Prevotella* sp of bacteria, rather than waiting for the patient to fail to respond. It is inappropriate to expose 10% to 30% of patients with pelvic infections to potential life-threatening complications such as abscess formation and septic pelvic thrombophlebitis.

FIGURE 8.2. Traditional approach to the treatment of mixed anaerobic-aerobic soft tissue pelvic infections.

A major turning point (as discussed previously) in the management of pelvic infections was the classic study by diZerega et al. (66), in which the benefits of this early aggressive approach in the therapy against resistant anaerobes were demonstrated to yield significant improvement in medical outcome and decreased hospital costs. Subsequently, Ledger (67) noted that although the traditional approach with ampicillin or a penicillin-aminoglycoside regimen resulted in clinical cures for 316 of 416 patients (76%), 8% of these patients required additional antimicrobial agents, 2% required heparin, and 14% required surgical intervention. With the use of a clindamycin-aminoglycoside or clindamycin-aminoglycoside-ampicillin regimen in 204 patients, the cure rate overall was 87%; 8% of these patients required additional antibiotics, but none required heparin for septic pelvic thrombophlebitis, and only 4.4% required surgical intervention. Similarly, in this review, the use of cefoxitin or third-generation cephalosporins effective against *B. fragilis* in 285 patients was associated with an overall cure rate of 85%; 8% of patients required additional antibiotics, 0.4% required heparin, and 4.9% required surgical intervention. Thus, in this large review, it was demonstrated that treatment effective against resistant anaerobic organisms resulted in a significant decrease in the need for anticoagulation for septic pelvic thrombophlebitis and surgical intervention for the management of abscesses.

Studies of pelvic infection that used antimicrobials that did not provide coverage for *B. fragilis* or other resistant anaerobes of the *Prevotella* sp have reported cure rates ranging from 70% to 90% but noted that these regimens result in a 5% to 29% occurrence rate of severe infections (e.g., pelvic abscess, wound abscess, or septic pelvic thrombophlebitis). On the other hand, studies that included antimicrobial regimens effective against resistant anaerobes such as *B. fragilis* and *B. bivius* reported cure rates in the 87% to 100% range and most significantly a lower incidence of severe infections, ranging from 0% to 15% (Fig. 8.3) (13). The availability of clindamycin, metronidazole, and new and safe blactam antimicrobial agents that are effective against organisms such as *B. fragilis, P. bivia,* and *P. disiens* and early therapy with either combinations of agents or single agents effective against both components of mixed anaerobic and facultative pelvic infections has reduced the incidence of serious complications of pelvic sepsis (e.g., pelvic abscess and septic pelvic thrombophlebitis).

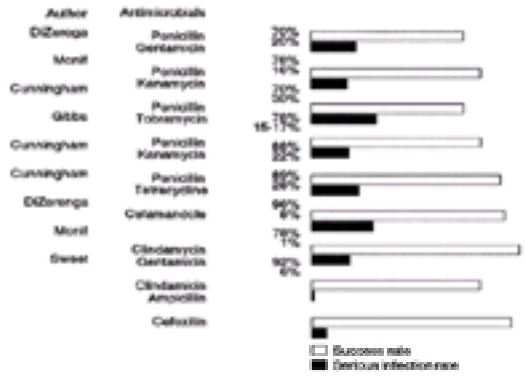

FIGURE 8.3. Treatment of soft tissue pelvic infections: clinical cure rates and

incidence of severe infection. Efficacy of antimicrobial regimens for post–cesarean section endomyometritis.

Various antimicrobial combinations and single antimicrobial agents provide effective therapy against the anaerobic bacteria, including *B. fragilis* and *Prevotella* organisms and many of the facultative bacteria associated with the infections of the female genital tract (Table 8.10). These include either clindamycin or metronidazole in combination with an aminoglycoside. Aminoglycosides have been the traditional choice for coverage of aerobic Gram-negative bacilli in soft tissue pelvic infections when combination therapy is chosen. Recently, once-daily aminoglycoside dosing has been proposed as an alternative to the traditional multiple dosing per day (1). This approach is based on two features of aminogylcosides: concentration-dependent bactercidal activity and a long postantibiotic effect (up to 7.5 hours) (1). This allows for a prolonged dosage interval, during which bacterial regrowth does not occur despite serum levels of the drug below the MIC. The new third-generation cephalosporins or aztreonam could be used in place of the aminoglycoside.

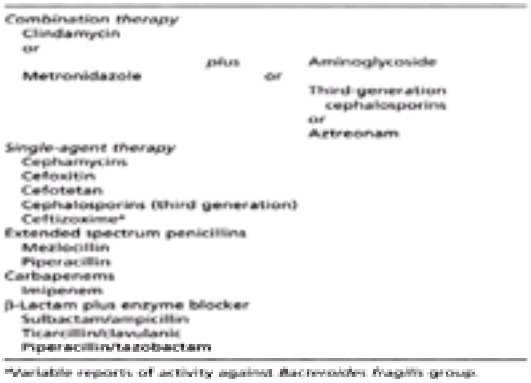

TABLE 8.10. POSSIBLE ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF MIXED ANAEROBIC-AEROBIC SOFT TISSUE PELVIC INFECTION

Various single agents are available with demonstrated efficacy in the treatment of mixed anaerobic-aerobic pelvic infections. These include the cephamycins, cefoxitin and cefotetan; possibly the third-generation cephalosporin, ceftizoxime; the extended-spectrum penicillins, mezlocillin and piperacillin; the carbapenem, imipenem; and the blactam plus enzyme blockers, sulbactam-ampicillin (Unasyn), ticarcillin–clavulanic acid (Timentin), and piperacillin-tazobactam (Zosyn). For pelvic infections, it would generally be unnecessary to add an aminoglycoside to these agents because of the paucity of *P. aeruginosa* as a pathogen in nonimmunosuppressed obstetric and gynecologic patients. The very high incidence of *B. fragilis* resistance to cefoperazone and cefotaxime (upward of 50%) demonstrated in national collaborative studies limits their use as single-agent therapy for serious mixed anaerobic-aerobic infections of the pelvis (53,54,55,56,57 and 58).

Imipenem is probably the optimum single agent for the treatment of soft tissue pelvic infections because it has the broadest spectrum of activity including some enterococci and *P. aeruginosa* (76,77). However, it is generally not used as a first-line drug but is reserved for severe infections. Increasing resistance by both Gram-negative facultative bacteria such as *E. coli* and anaerobes such as the *B. fragilis* group and *Prevotella* sp has also limited the use of piperacillin and mezlocillin as single-agent therapy for soft tissue pelvic infections. To address the issue of increasing resistance to formerly effective and safe blactam antibiotics, the novel approach of combining an enzyme blocker to these agents emerged. The parenterally available agents in this group included ampicillin-sulbactam (Unasyn), ticarcillin–clavulanic acid (Timentin), and piperacillin-tazobactam (Zosyn). Clinical studies have confirmed the efficacy of these agents in the treatment of soft tissue pelvic infections (82,83 and 84). These agents are discussed in greater depth in Chapter 23 (Antimicrobial Agents).

In approximately 1% of pelvic infections, patients fail to respond to appropriate antimicrobial therapy and do not have an abscess or hematoma requiring surgical intervention. In these patients, a diagnosis of septic pelvic thrombophlebitis should be considered. Heparin therapy is commenced (antimicrobial therapy is continued) as both a diagnostic and therapeutic tool. The goal is to achieve a partial thromboplastin time that is 2.5 times that of the control. If the diagnosis is correct, the patient should rapidly respond and become afebrile within 24 to 36 hours. Heparin therapy is continued for 10 days, unless septic pulmonary emboli occur. In this circumstance, long-term anticoagulation is necessary.

At times, the best antimicrobial agent for the management of pelvic infections is the competent surgeon who applies prophylactic antibiotics properly, uses good surgical technique, and uses surgical drainage and excision of necrotic tissue when appropriate. The clinician caring for women with pelvic infections must recognize that surgical intervention is often the critical factor for resolution of pelvic soft tissue infection associated with mixed anaerobic-facultative bacteria. Investigators at the Tufts New England Medical Center have demonstrated a significant improvement in mortality rates in patients with intraabdominal abscesses (85). These investigators suggested that the improved survival rate among patients with intraabdominal abscesses was due to earlier diagnoses being made, the employment of aggressive broad-spectrum antimicrobial treatment, which included agents effective against *B. fragilis* and other resistant Gram-negative anaerobes, and the use of early surgical intervention when the patient did not respond to antimicrobial therapy. Anaerobic bacteria are recognized as pathogens in the pathogenesis of pelvic and intraabdominal abscesses. These abscesses are unique anaerobic environments in which there is an extremely low oxidation-reduction potential and a low pH level. As a result, white blood cells (WBCs) cannot phagocytose and cannot kill bacteria. In addition, an abscess contains many microorganisms, in the range of 10^7 to 10^9 organisms per milliliter. This results in an inoculum effect, in which although *in vivo* testing with 10^5 organisms shows susceptibility, the *in vivo* situation is very different. Finally, this abscess environment provides sufficient opportunity for the microorganisms to produce a multitude of inactivating enzymes that preclude activity of various antimicrobial agents. This is the mechanism by which chloramphenicol is rendered inactive inside an abscess environment. In addition, many of the penicillins and first-generation cephalosporins are inactivated by the b-lactamase enzymes produced by this multitude of bacteria. Of the antimicrobial agents available, animal model studies have demonstrated that clindamycin, cefoxitin, moxalactam, and metronidazole penetrated into the abscess environment in sufficient quantities to be

effective (86).

In the past, the general consensus held that pelvic abscesses required surgical intervention. However, recent studies have demonstrated that such a dictum is not necessarily true, particularly for TOAs (87,88 and 89). In our series of TOAs in the group of women receiving antibiotics effective against *B. fragilis,* nearly 70% of these abscesses responded to antimicrobial therapy alone, without surgical drainage (87). It is our feeling that antimicrobial therapy as the first step is appropriate in the management of these abscesses and that either clindamycin, metronidazole, or cefoxitin should be the antimicrobial agent used because of the demonstrated penetration into and stability within the abscess environment.

Summary: Anaerobic-Aerobic Infection

The selection of antimicrobial agents for gynecologic and obstetric patients with mixed aerobic-anaerobic pelvic infections must be based on knowledge of the microorganisms involved. It is now recognized that infections of the female upper genital tract are due to multiple bacterial organisms. In general, these infections are associated with mixtures of anaerobic bacteria, particularly *Peptostreptococcus* sp, *B. fragilis, P. bivia, P. disiens,* and *P. melaninogenica*; the facultative Gram-negative Enterobacteriaceae, particularly *E. coli*; and facultative streptococci.

In clinical situations, the choice of antimicrobial agents must often be empiric and must be based on known susceptibility patterns of the microorganisms generally recognized to be involved in gynecologic and obstetric infections. A major advance in the approach to the treatment of mixed aerobic-anaerobic pelvic infections has been the recognition that early treatment that effectively eradicates Gram-negative anaerobic bacilli (*B. fragilis, P. bivia,* and *P. disiens*) results in higher cure rates and lower incidences of severe infection, such as pelvic abscesses, bacteremia, and septic pelvic thrombophlebitis than the traditional approach to treatment with regimens such as ampicillin, a first-generation cephalosporin, or a penicillin-aminoglycoside combination. This more aggressive approach will result in prevention of significant morbidity and, hopefully, the occasional mortality that still occurs on obstetric and gynecologic services due to infection.

Pelvic Abscess

Despite the introduction of many new and potent broad-spectrum antimicrobial agents for the treatment of pelvic infections and the widespread use of prophylactic antibiotics in surgical procedures, pelvic abscesses remain a diagnostic and therapeutic challenge for obstetrician-gynecologists (1,2,3,4,5,6 and 7). Pelvic abscesses can be categorized on the basis of etiologic origin (3). The major types of pelvic abscess include (a) those that occur secondary to ascending intracanalicular spread of microorganisms from the cervix via the endometrial cavity to the adnexa (i.e., TOA), (b) those that arise after puerperal infections via lymphatic or hematogenous spread from the endometrium or myometrium to the adnexa, (c) those that are an infectious complication of pelvic surgery, and (d) those that may be secondary to infection in ongynecologic pelvic organs (e.g., appendicitis or diverticulitis).

Although pelvic abscesses constitute a small proportion of gynecologic inpatient

admissions or hospital-acquired infections on obstetric and gynecologic services, they are among the most serious complications seen by practicing obstetrician-gynecologists and are associated with prolonged hospitalization, significant morbidity, and adverse effects on the reproductive health of young women. TOAs have been reported to constitute 1.6% to 2.2% of gynecologic admissions at urban public hospitals (8,9) and have been noted to occur in 3% to 16% of patients hospitalized with acute PID (4,7,10,11). In the case of hospital-acquired infection after pelvic surgery, the reported incidence of pelvic abscess formation in the era before widespread use of prophylactic antibiotics ranged from 0.7% to 2.0% (12,13 and 14).

Postoperative Abscess

The frequency of postoperative soft tissue pelvic infections has been reduced by the use of prophylactic antibiotics (Chapter 24, Antibiotic Prophylaxis in Obstetrics and Gynecology). However, they remain a significant problem for the clinician, particularly when abscess formation occurs posthysterectomy.

Posthysterectomy abscesses are divided into two major categories. The vaginal apex cuff abscess or infected hematoma usually presents with fever and a sensation of fullness or vague discomfort in the lower abdomen. Examination typically discloses an infected, foul-smelling collection that is extraperitoneal and can be easily drained per vagina with resultant prompt response. Cuff abscesses characteristically present after 48 hours postoperatively but during the initial hospitalization. Hevron and Llorens (12) reported the occurrence of 36 cuff abscesses among 1,600 major pelvic operations (2%) and noted that cuff abscess drainage occurred on an average of 8 days after surgery.

The second group of posthysterectomy abscesses includes the true intraperitoneal pelvic abscesses, which tend to present at a later time, often after initial discharge from the hospital (12,13). As noted by Ledger et al. (13), posthysterectomy adnexal abscesses may occur up to 133 days postsurgery. In the preprophylactic antibiotic era, postoperative pelvic abscesses had been reported to occur in 13 (0.7%) of 1,600 major pelvic operations by Hevron and Llorens (12) and in 1% of patients undergoing hysterectomy by Ledger et al. (13). In the Ledger et al. series, nearly 3% of patients who had a vaginal hysterectomy (preprophylactic antibiotic use) developed adnexal abscesses requiring surgical intervention. In both of these series, most postoperative abscesses occurred after vaginal hysterectomy. These abscesses present with abdominal pain, fever, and a tender, palpable pelvic mass. Characteristically, posthysterectomy adnexal masses are high in the pelvis. Although they may, on occasion, respond to antimicrobial therapy, our recommendation for the management of posthysterectomy adnexal abscesses is to initiate antimicrobial therapy, which includes coverage for resistant anaerobes such as *B. fragilis* and to promptly proceed to exploratory laparotomy for extirpation or drainage of infected tissues. As noted by Hevron and Llorens (12), vaginal drainage is not the optimal approach for management of posthysterectomy abscesses. They reported that of nine cases of postoperative pelvic abscess with primary treatment via vaginal drainage, five (55%) required subsequent laparotomy for eradication of infection (12). An alternative approach is drainage of a pelvic abscess by percutaneous computed tomography (CT)–guided or ultrasound-guided drainage. Although success rates for percutaneous catheter drainage (PCD) of well-defined unilocular abscesses are excellent, with 80% to 90% success rates reported (15,16 and 17), cases of more

complex abscesses (loculated, poorly organized, or extensive collections of abscesses) such as those seen in the pelvis have been less successful and associated with higher rates of complications (18). Gerzof et al. (18) reported a success rate of 43% for PCD of complex cases, compared with 82% with simple abscesses. Moreover, the complication rate was fourfold higher with PCD of complex abscesses (21% vs. 5%) (18). Recent studies using improved real-time ultrasound technology have reported excellent cure rates with ultrasound-guided percutaneous (19), endovaginal (20), and transrectal (21) drainage techniques.

Tuboovarian Abscess

One of the major complications or sequelae of acute PID is the TOA (22). TOA has been reported to occur in 34% of patients hospitalized with salpingitis (4,7,23,24,25,26,27 and 28). Although the TOA has been referred to as an end stage in the progression of upper genital tract infections (27,28), a number of studies have shown that a prior history of PID is obtained in only one third to one half of patients presenting with a TOA (4,28,29 and 30). This may indicate that subclinical infections are more prevalent than suspected or that upper genital tract infections may progress to abscess stage during the initial presentation, possibly dependent on the organisms involved.

Diagnosis

Clinical Findings

TOAs occur most commonly in the third and fourth decades of life (23,28,31,32 and 33). The parity of these patients is variable, with approximately 25% to 50% being nulliparous (4,23,28,29 and 30).

Abdominal or pelvic pain is the most frequent presenting complaint and was the major complaint in more than 90% of patients with TOAs reported in the literature (4,24,28,31, 32). Landers and Sweet (4) reported that of 232 patients with TOAs, a complaint of fever and chills was elicited in 50%; vaginal discharge, 28%; nausea, 26%; and abnormal vaginal bleeding, 21%. A number of investigators have reported on the incidence of fever and leukocytosis, but definitions were variable. Temperature of at least 100.1°F, and usually higher, has been reported in 60% to 80% of patients; and leukocytosis, although often undefined, was reported in 66% to 80% of patients (4,23,24,29,31,32). A clinically significant finding is that many patients harboring TOAs may present with temperatures and WBC counts in the normal range. In the series reported by Landers and Sweet (4), 35% of patients with surgically confirmed TOAs were afebrile, and 23% had a WBC count in the normal range. Thus, the absence of fever or leukocytosis should not, by itself, exclude a diagnosis of TOA.

In general, the presenting clinical findings for patients with uncomplicated PID (i.e., no inflammatory mass) and for those with TOAs are similar. Differentiation requires determination of the presence of an inflammatory adnexal mass. This illustrates the importance of recognizing the presence of an adnexal or a pelvic mass in patients presenting with the signs and symptoms of acute PID. Physical examination alone may often be insufficient because pain and tenderness may preclude an adequate pelvic examination. Several relatively noninvasive imaging techniques may be used

to aid in the diagnosis of pelvic abscesses and should be used whenever suspicion of an abscess arises. Differentiation of a TOA from inflammatory masses with adherent bowel or omentum is appreciably improved with such techniques. Laparoscopy may also be helpful as a diagnostic clinical tool, particularly when the diagnosis is in question.

Imaging Techniques

Several noninvasive imaging techniques are available to facilitate the diagnosis and management of patients suspected of having abdominal or pelvic abscesses (20,34,35,36,37,38,39,40,41,42 and 43). These include radionuclide scanning, scintigraphy, ultrasound (sonography), and CT. The commonly employed radionuclide scans, gallium-67 (^{67}Ga)–labeled and indium-111 (^{111}In)–labeled WBC scanning, have been highly accurate in the localization of intraabdominal abscesses (36,37,38 and 39). Although they are easy to perform, they are expensive, require 24 to 48 hours' delay before interpretation (^{67}Ga), and produce false-positive scans due to the high affinity of these radionuclides to inflammatory tissue, such as infected or neoplastic tissue, rather than just discrete abscesses. The sensitivity of gallium scanning for detecting intraabdominal sepsis is poor and this procedure is not generally used for this purpose. The most accurate radionuclide technique for diagnosing abscesses seems to be ^{111}In-labeled WBC scans, with a reported accuracy of 87% (38). More recently, alternative WBC labeling agents have been assessed. Technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) appears to be the most promising (44). The major advantage of this technique is that scanning can be performed 4 hours after administering the agent, compared with 24 hours for ^{111}In oxine–tagged WBC with equivalent sensitivity (45). None of the radionuclide scanning techniques have been well studied for diagnostic accuracy in patients with TOAs.

An additional technique is scintigraphy with radiolabeled polyclonal immunoglobulin G (IgG). For detecting acute infectious processes, the sensitivity and specificity of scanning with In-labeled polyclonal IgG is 90% and 95% to 100%, respectively (46,47). However, for detecting subacute or chronic infections, the sensitivity drops to 74%, whereas the specificity remains high (48).

It appears that radionuclide scanning is most useful in patients with localized signs of infection. However, even when radionuclide scanning identifies a focus of intraabdominal infection, further evaluation by CT or ultrasound is often required for more definitive localization of the infectious process or for guidance of PCD (16). Thus, for suspected pelvic (and intraabdominal) abscesses, the most appropriate imaging investigations remain ultrasound or CT.

Ultrasonography has become a frequently used confirmatory test when the diagnosis of a TOA is suspected; this relatively inexpensive scan can be useful in both confirming the clinical impression and measuring response to therapy. A number of retrospective studies have looked at the accuracy of ultrasound in the diagnosis of pelvic abscesses (34,40,41,42 and 43). The largest of these, by Taylor et al. (40), included 220 patients with surgically proven abdominal or pelvic abscesses. In this series, 36 of 40 abdominal and 32 of 33 pelvic abscesses were correctly identified, whereas 112 of 113 suspected abdominal and 33 of 34 suspected pelvic abscesses were correctly ruled out. Landers and Sweet (4) reported a series of 98 patients who were evaluated with ultrasound, of which 31 had surgically confirmed TOAs.

Twenty-nine of 31 surgically confirmed TOAs had been reported as complex adnexal masses or cystic-type masses with multiple internal echoes and were felt to be consistent with an abscess. The remaining two were simple cystic masses. A mass was correctly identified in all surgically confirmed TOAs and in 90% of the 67 patients with clinically diagnosed TOAs (4). Ultrasound of a TOA reveals a discrete mass, with internal echoes indicating its complex nature. A sonogram of a surgically documented TOA is shown in Fig. 8.4. Ultrasound may also be useful in assessing response to therapy by detecting changes in the size and architecture of these masses. As technology has improved the quality of ultrasound, and ultrasonographers gain experience with techniques that combine the use of real-time and static imaging, the accuracy of this technique in the diagnosis and management of TOAs has been further enhanced. In summary, for the pelvis, transabdominal ultrasound has a sensitivity of 90% or more for detecting a pelvic abscess (49). The advent of endovaginal ultrasonography has further enhanced the sensitivity and specificity of ultrasound confirmation of pelvic abscesses (20).

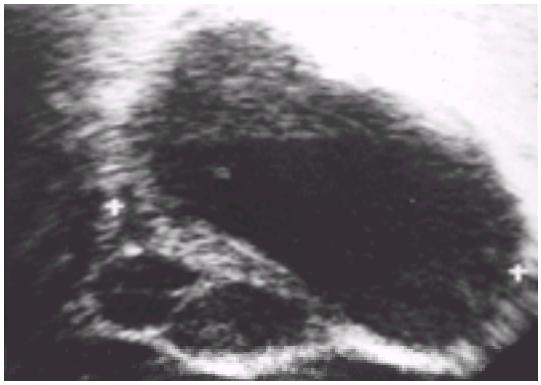

FIGURE 8.4. Ultrasound scan demonstrating a large left tuboovarian abscess, which subsequently required surgical extirpation.

CT scans have been used extensively, in the diagnosis and the treatment of abdominal abscesses. For intraabdominal abscesses, CT is superior to ultrasound but more costly (50). CT has a sensitivity of 78% to 100%, compared with a sensitivity of 75% to 82% for ultrasound (50,51). There is, however, very little information available on the accuracy of these scans, specifically for the diagnosis of TOAs or other pelvic abscesses. Moir and Robins (43) compared the accuracy of ultrasound, gallium, and CT scanning in the diagnosis of abdominal abscesses. They reported the sensitivity of ultrasound, gallium, and CT as 82%, 96%, and 100%, respectively. Specificity was reported as 91%, 65%, and 100%, respectively. Thus, CT scans appear to be very accurate, at least in the abdomen, in detecting the presence of an abscess. It is unclear whether the sensitivity and specificity in the pelvis are similar and whether the increased accuracy of CT justifies the expense. Our current approach is to obtain ultrasound as the initial diagnostic aid and reserve CT scans for those patients in whom ultrasound fails to provide adequate information. A large pelvic abscess is seen on a CT scan in Fig. 8.5. Magnetic resonance imaging (MRI) may play a role in diagnosing intraabdominal and pelvic abscesses. To date, there is very limited experience with MRI in the evaluation of

pelvic masses. Only MRI clinical experience can determine whether the theoretic advantages in accuracy with MRI are applicable to clinical use in differentiating pelvic masses and whether the increased cost is balanced by increased diagnostic accuracy.

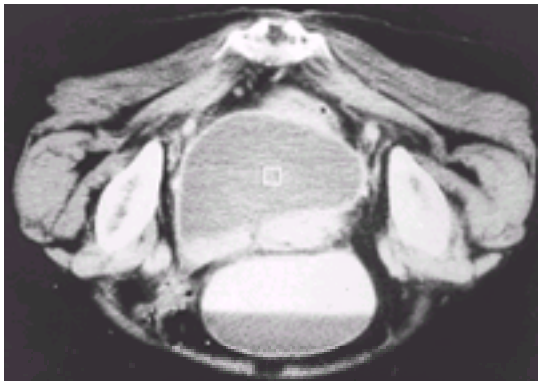

FIGURE 8.5. Computed tomographic scan demonstrating a large pelvic abscess.

Etiology and Pathogenesis

Microbiology of TOAs

The microbiology of TOAs is predominantly a mixed flora of anaerobes and facultative or aerobic organisms (4,5,52). Anaerobic organisms are particularly prevalent in these abscesses, having been isolated from 63% to 100% of adnexal abscesses in which appropriate anaerobic microbiologic technology was used (4,5,53,54,55,56,57 and 58). The major role played by anaerobes in TOAs was initially demonstrated by Altimeter in the early 1940s, when he isolated anaerobic organisms from 92% of the TOA specimens that had been previously reported by the clinical laboratory as “no growth” (55). More recently, Landers and Sweet reported that the predominant organisms isolated from TOA aspirates were *E. coli* (37%), *B. fragilis* (22%), other *Bacteroides* (now *Prevotella*) sp (26%), aerobic streptococci, *Peptococcus* (11%), and *Peptostreptococcus* (18%) (4). These are many of the same organisms noted to be involved in a biphasic aerobic-anaerobic animal model of intraabdominal sepsis and abscess formation developed by Weinstein et al. (58). In this model, the organisms recovered from these abscesses were predominantly anaerobes, particularly *B. fragilis* and *Bacteroides* sp. Thus, anaerobic organisms, in particular *B. fragilis*, seem to be strongly associated with abscess formation. The concept of the “sterile abscess” is a misnomer. These reported sterile abscesses probably reflect either inappropriate specimen procurement or lack of appropriate anaerobic microbiology techniques. The report by Landers and Sweet (4) significantly underestimates the prevalence of anaerobic bacteria, particularly *B. fragilis* and *Prevotella* sp because many of the abscesses were managed before establishment of the research anaerobic microbiology laboratory at their institution.

One of the virulence factors associated with *B. fragilis* seems to be related to its

capsular polysaccharide. A number of *Bacteroides* organisms failed to produce significant numbers of abscesses in experimental rats; however, when encapsulated *B. fragilis* was used alone, 95% of the rats developed abscesses (59). It has further been shown that encapsulated strains of *B. fragilis* are more resistant to opsonophagocytosis than other *Bacteroides* sp (60). Thus, not only are *B. fragilis* strains by themselves capable of causing abscesses, but even the capsular polysaccharide of *B. fragilis* potentiates abscess formation. In addition, the virulence of anaerobes may be due to the various enzymes they produce (61). Among these enzymes are collagenases and hyaluronidases, which may prevent walling off of infection, and heparinase, which may promote clotting in small vessels and may further decrease blood supply to infected tissue and consequently decrease oxygenation of the infected area. Superoxide dismutase, which is also produced by some anaerobes, may assist these anaerobes in surviving under aerobic conditions. Recent investigations have emphasized the emergence and recognition of *P. bivia* and *P. disiens* as major pathogens in infections of the upper female genital tract (4). *P. bivia,* and to a lesser degree *P. disiens,* is a major component of the normal vaginal-cervical flora and thus is not unexpectedly present as frequent pathogens on obstetric and gynecologic services.

In the past, *N. gonorrhoeae* was considered to be *the* major pathogen in the etiology of PID. Current opinion holds that the etiology of acute PID is polymicrobic, with *N. gonorrhoeae, C. trachomatis,* and mixed anaerobic-aerobic bacteria involved. The recovery of *N. gonorrhoeae* from TOAs is very uncommon. Landers and Sweet recovered *N. gonorrhoeae* from only 3.8% of 53 TOA aspirates, although the overall recovery rate of this organism from the endocervix was 31% (4). *C. trachomatis* is now recognized as a major etiologic agent in acute salpingitis. However, the role of this organism in TOAs has not been determined. In our experience, *C. trachomatis* has never been isolated from a TOA.

Actinomycetes, most commonly *Actinomyces israelii*, a Gram-positive anaerobe, have occasionally been recovered from patients with PID, particularly in association with TOAs. A relationship between these organisms and IUD use has been suggested by several investigators (62,63 and 64). Burkman et al. (25) noted that PID associated with the presence of actinomycetes was more likely to be increased in clinical severity. Seven of eight (87.5%) of their patients with PID with actinomycetes present had a TOA, compared with 11 of 38 (28.9%) patients with PID without actinomycetes. However, these organisms have not been recovered in several TOA series (4,31,52). However, these organisms are very difficult to culture, often requiring maintenance of anaerobic conditions for as long as 2 weeks. Most actinomycetes are actually identified by histology in pathology specimens or by cytology on Papanicolaou smears. Although actinomycotic infections have been stereotypically characterized by fistula formation with chronic draining sinuses, as Schmidt et al. (65) pointed out, the clinical diagnosis of actinomycetes in genital tract infections is seldom made before surgery. The exact role of actinomycetes in abscess formation remains unclear, as does the mechanism of their apparent relationship to the IUD. Whether *A. israelii* is a sole pathogen or a marker for mixed anaerobic-facultative infection is unclear. If actinomycetes are demonstrated in association with a TOA, long-term antibiotic therapy for 6 weeks to 3 months should follow surgical extirpation of the infected tissue. Penicillin is the drug of choice; cephalosporins, clindamycin, cefoxitin, or chloramphenicol are alternative agents.

Pathogenesis of TOAs

The mechanism by which TOA formation occurs is difficult to establish because of the various presentations and degrees of tubal damage present when the infection is noted. Studies done with the gonococcus have demonstrated that once it ascends to the fallopian tube, it attaches to the mucosal epithelial cells, penetrates the epithelial cells via phagocytosis, and causes the destruction of the epithelial cells. The destruction of the endosalpinx results in the production of a purulent exudate. In addition, the gonococci may extend from the mucosa through the subepithelial tissue to involve the muscularis and the serosa of the fallopian tube in the inflammatory process (66). Hare and Barnes (67) have demonstrated that *B. fragilis* organisms are more virulent than gonococci in fallopian tube explant systems. Within 4 days of inoculation into the explant system, *B. fragilis* organisms destroyed the tubal epithelium (67). In the early stages of disease, the tubal lumen is open, and the purulent exudate exudes from the fimbriated end, resulting in peritonitis. During this initial inflammatory phase or during a recurrent infection, the ovary (and other pelvic structures) may become involved in the inflammatory process. Presumably, an ovulation site in the ovary serves as the portal of entry for organisms into the ovary, with subsequent tissue invasion. Eventually, tissue planes become lost, and the separation of tube and ovary is obscured as the abscess forms. The abscess may remain localized, with involvement of the tube and ovary alone. It may involve other contiguous pelvic structures, such as bowel, bladder, or the opposite adnexa, which may be undergoing similar inflammatory changes. At any point in the progression, rupture may occur.

As discussed in Chapter 14 (Pelvic Inflammatory Disease), *C. trachomatis* (unlike *N. gonorrhoeae* and anaerobic bacteria) does not produce its damage through an acute inflammatory and exudative process. Rather, *C. trachomatis* produces damage to the fallopian tube via the cell-mediated immune response to chlamydial heat shock protein (68). Thus, it is not surprising that *C. trachomatis* has not been recovered from TOAs.

IUD Use and Tuboovarian Abscesses

The frequency of IUD usage in patients presenting with TOAs has been reported to range from 20% to 54% (29,30,52,69,70 and 71). In the mid-1970s, it was believed that there was a strong correlation between IUD use and the development of unilateral TOAs. Taylor et al. (72) reported 16 patients who developed unilateral TOAs while wearing an IUD or soon after its removal. Dawood and Birnbaum (73), in the same year, reported four additional cases and stressed the IUD association with unilateral TOAs as a distinct clinical entity. Subsequent investigation by Golde et al. (52) suggested that unilateral TOAs were a distinct entity, with or without an IUD. They did, however, report that 62.5% of IUD users with TOAs had unilateral disease, compared with 32.1% in nonusers. Several investigators have since compared the incidence of unilateral abscesses in IUD users with that of nonusers (4,29,30,70,71). These results and those of Golde et al. (52) are summarized in Table 8.11. In these studies, the incidence of unilateral TOAs ranged from 20% to 71%. The incidence of unilateral TOAs in IUD users was 25% to 89%. Thus, there was little difference in the incidence of unilateral TOAs with or without IUD use in most of these studies.

Study	No. of TOAs	No. of Unilateral TOAs (%)	No. of TOAs in IUD Users (% Unilateral)	No. of TOAs in Nonusers (% Unilateral)
Landers and Sweet (4)	232	164 (71)	76 (71)	156 (70.5)
Ginsberg et al. (29)	160	90 (56)	75 (61)	85 (52)
Edelman and Berger (30)	318	65 (20)	67 (25)	251 (19)
Golde et al. (52)	85	35 (43.5)	32 (62.5)	53 (32)
Scott (70)	66	28 (42)	19 (42)	47 (43)
Manara (71)	41	29 (71)	9 (88)	32 (66)
Total	902	411 (46)	278 (59)	624 (42)

TOA, tuboovarian abscess; IUD, intrauterine device.

TABLE 8.11. INCIDENCE OF UNILATERAL TOAs IN IUD USERS AND NONUSERS

The pathogenesis of IUD-related salpingitis and adnexal abscess formation has yet to be clearly demonstrated. Several investigators have offered tenable hypotheses; however, none of these alone can account for the diversity of clinical manifestations associated with IUD-related infections. Burnhill (74) suggested in 1973 that a syndrome of progressive endometritis was associated with IUDs in which menorrhagia, metrorrhagia, and leukorrhea were noted and were followed by progressive endometritis, parametritis, peritonitis, and pelvic abscess formation. It has become clear that bacterial colonization of the endometrium is not merely a result of contamination at the time of insertion (75). The currently accepted hypothesis is that the IUD tail, projecting through the cervical canal, allows easy access of vaginal bacteria to the upper genital tract. In 1981, Sparks et al. (76) published a series of 22 IUD users undergoing hysterectomy who were evaluated by a multiple biopsy technique. They found bacteria in the uterus in 15 of 17 women with tailed IUDs. They also noted that all five uteri with a tailless IUD were sterile. They found no difference in bacteria counts between monofilamentous and multifilamentous devices. In another study (77) published in 1982 in which a group of 33 baboons with IUDs were studied, the multifilament tail and particularly the cracked multifilament tails were associated with considerably greater intrusion of bacteria into the uterine cavity than the monofilament tail. This difference was not related to the type of IUD (Lippes loop, Dalkon shield). Persistence of bacterial flora in the uterine cavity, combined with a breakdown of the host defense mechanisms, may be enough to cause chronic endometritis, with progressive spread either by intracanalicular spread from the endometrium to the fallopian tubes or ovary or less likely via lymphatics in the parametrium and broad ligament to involve the adnexa.

Treatment Approach

Medical Therapy of TOAs

Contemporary management of TOAs challenges the traditional dictum that abscesses cannot be adequately eradicated by antibiotics alone and require surgical drainage or extirpation. Saini et al. (78) at the Tufts New England Medical Center attributed the improved survival of patients at their institution with intraabdominal abscesses to the combination of earlier diagnosis and improved localization of

abscesses (with the use of newer imaging techniques such as real-time sonography and CT), earlier drainage, and the use of broad-spectrum antimicrobial regimens effective against anaerobes, particularly *B. fragilis.* However, the issue is whether a TOA can be treated conservatively, without significant risk to the patients, in the hope of preserving fertility and ovarian function. There is general acceptance that rupture of a TOA is an emergency and an indication for immediate surgical intervention. However, the management of the unruptured TOA has evolved dramatically over the past 20 years. Opinions range from prompt surgical intervention, with complete removal of the uterus and adnexa (24,79), to treatment with intravenous antibiotics, in which surgery is reserved for patients who fail to respond or in whom there is suspicion of rupture (4,28,29). A frequent approach in the era when antibiotics first became available (1950s and 1960s) was long-term antibiotic therapy up to 21 days for the acute stage, followed by 3 to 6 months of "cooling off" and ultimately a total abdominal hysterectomy and bilateral salpingo-oophorectomy during the "chronic, burned-out" stage. More recently, it has also been suggested that in those patients with unilateral TOAs requiring surgical intervention, unilateral adnexectomy may be an appropriate alternative in terms of preserving future fertility and hormonal production (8). Landers and Sweet (4) questioned whether unilateral adnexectomy is further indicated in hopes of preventing future flare-ups and improving future fertility on the contralateral uninvolved side.

Kaplan et al. (79) treated 71 patients with total abdominal hysterectomy and bilateral salpingo-oophorectomy within 24 to 72 hours of instituting antibiotics. With this aggressive approach, bowel injury (serosal tears) occurred in 8.4% of patients. Such an approach, although often curative, eliminates future reproductive or hormonal function. It would seem prudent to question whether such an aggressive approach is necessary in all patients with TOAs. Several investigators have since reported favorable results, with a more conservative approach aimed at preservation of future reproductive potential (4,7,28,29,80).

Table 8.12 summarizes studies using conservative medical therapy as the initial approach to the management of the unruptured TOA. Franklin et al. (28) reported the results of 120 patients treated with an initial conservative approach. Eighty-five patients were treated with antibiotics alone, and 35 patients were treated with antibiotics plus colpotomy drainage. The overall failure rate was 26.5%, of which 10% were early failures. Ninety-seven patients were followed between 2 and 8 years after discharge, with a subsequent intrauterine pregnancy rate of 10.3% (28). In 1980, Ginsberg et al. (29) reported a series of 160 patients initially treated with antibiotics alone, of which 31% were early failures and 35% were late failures. Long-term follow-up, ranging from 1 month to 10 years, was obtained in 95 patients; the subsequent intrauterine pregnancy rate was 9.5% (29). In a group of 232 patients with TOAs, Landers and Sweet (4) reported that 217 were treated initially with antibiotics alone. Early failure was seen in 19.4%, and late failure in 31%. Long-term follow-up data, more than 2 years, were available in 58 patients, and the subsequent intrauterine pregnancy rate was 13.8%. Hemsell et al. (80) reported that cefotaxime treatment of TOAs resulted in 95% of patients with TOAs responding to antibiotic therapy alone. Readmission for surgery was subsequently necessary in 12%. Reed et al. (6) reported their findings comparing cefoxitin-doxycycline with clindamycin-gentamicin for the treatment of TOAs. These authors (6) found that 90 (75%) of 119 TOAs responded initially to medical therapy alone, with equivalent results noted with both antimicrobial regimens. Recently, McNeeley et al. (7) compared cefotetan-doxycycline, clindamycin-gentamicin, and

ampicillin-clindamycin-gentamicin in the treatment of TOAs. Overall, they reported that 52 (70%) of 74 TOAs responded to antibiotic therapy alone. However, unlike Reed et al. (6), they (7) demonstrated that triple therapy (clindamycin-gentamicin-ampicillin) was significantly more effective (87.5%) than cefotetan-doxycycline (34%) and clindamycin-gentamicin (47%) (p = 0.001). Taken together, these studies demonstrate a response to medical therapy in 69.4%, with a range of 16% to 95%. The rate of subsequent intrauterine pregnancy ranged from 9.5% to 15%, with an 11.3% rate overall. This is a minimum and overly pessimistic estimate of fertility chances because those women using contraception are not excluded. For example, Hager (26) reported a 50% pregnancy rate among patients with TOAs treated medically and who attempted to become pregnant.

Author	No. of TOAs Treated	No. with Response (%)	No. with Subsequent Pregnancy of Patients with Follow-up (%)
Landers and Sweet (6)	217	175 (81)	8/58 (13.8)
Franklin et al. (28)*	120	110 (92)	10/108 (9.3)
Ginsberg et al. (29)*	110	76 (69)	9/95 (9.5)
Edelman and Berger (30)	318	175 (55)	NS
Scott (70)	33	24 (73)	NS
Manara (71)	26	11 (42)	1/26 (3.8)
Hager (26)	32	5 (16)	4/8 (50)
Hemsell et al. (80)	41	39 (95)	6/41 (15)
Reed et al. (6)	119	90 (75)	NS
McNeeley et al. (7)	74	52 (70)	NS
Total	1090	757 (69.4)	38/336 (11.3)

TOA, tuboovarian abscess; NS, not significant.
*Includes some patients treated with colpotomy drainage.

TABLE 8.12. STUDIES USING CONSERVATIVE MEDICAL THERAPY AS THE INITIAL APPROACH TO MANAGEMENT OF TUBOOVARIAN ABSCESS

It may be difficult, clinically, to distinguish a TOA from a pyosalpinx, ovarian abscess, or some other inflammatory complex. This becomes less crucial when patients are treated with a conservative approach, as the initial therapy would be appropriate for any of these pelvic inflammatory masses. Future reproductive capability is a significant concern to most patients with TOAs and plays a major role in the desire for a more conservative approach to therapy.

Various antibiotic regimens were employed in the major reviews of TOAs in which the therapeutic regimens were stated. In the series by Franklin et al. (28), patients were treated primarily with penicillin and streptomycin. However, concomitant colpotomy drainage was performed in some patients. Ginsberg et al. (29) did not specifically state antibiotic regimens, except to say patients were treated with “broad-spectrum antibiotics, with multiple agents being employed frequently.” Manara (71) evaluated patients treated with intravenous penicillin plus an aminoglycoside. Of their 41 patients, 25 were treated initially with antibiotics alone, of which 15 (60%) failed to respond. Hager (26) recently reported the results of 32 patients with TOAs treated in the early 1970s initially with parenteral penicillin or a first-generation cephalosporin in combination with an aminoglycoside. Anaerobe coverage (unspecified, but presumably clindamycin or chloramphenicol) was added in most patients with an abscess. They reported clinical improvement, defined as afebrile, with a decrease in size of abscess in only 15.6%. Table 8.12 is a summary

of conservative antibiotic therapy of TOAs. From these data, there appears to be a tremendous variation in response rates to antimicrobial therapy alone. This confusion relates in part to the various definitions for response and the degree of aggressiveness in using surgical intervention. A major disadvantage in most of these studies was the lack of detailed analysis comparing responses to particular antibiotic regimens. If one accepts that these abscesses contain high concentrations of the resistant Gram-negative anaerobes, such as *B. fragilis, P. bivia,* and *P. disiens,* then improved results should be noted in patients treated aggressively with antibiotics effective against these resistant Gram-negative anaerobes, such as clindamycin, metronidazole, cefoxitin, moxalactam, other third-generation cephalosporins, possibly the extended-spectrum penicillins, and the b-lactamase inhibition combinations.

In the Landers and Sweet (4) series of 232 TOAs (1970 to 1980), treatment regimens varied. Patients treated in the earlier years received high-dose penicillin. In later years, an aminoglycoside was added, and the dose of penicillin was reduced. More recently, patients were treated primarily with combination therapy, which included clindamycin and an aminoglycoside. Response to therapy was determined on the basis of improvement in symptoms, absence of fever, reduction of pelvic tenderness, and decrease in size of the mass. Because all patients not requiring surgery during the initial hospitalization became afebrile with symptomatic improvement, evaluation of the mass was used to assess differences in therapeutic response.

The results of this evaluation are summarized in Table 8.13. Of the patients treated with antibiotics alone, 167 were examined before discharge. Reduction in mass size was seen in 25% of patients treated with penicillin alone, 49% of patients treated with penicillin and an aminoglycoside, and 68% of patients treated with regimens that included clindamycin ($p < 0.01$). A total of 104 patients who were available for follow-up were treated with antibiotic regimens that did not include clindamycin. The response rate was 36.5%, compared with the 68% response rate of the 63 patients treated with regimens that included clindamycin. The opposite trend was noted when examining those with an increase in mass size. Forty-two patients required surgical extirpation of an abscess during the initial hospitalization because of failure to respond to antimicrobial therapy alone. Of these, 64% were treated with regimens not containing clindamycin, compared with the 36% that received clindamycin-containing regimens. Of the patients treated with antibiotics alone, 134 returned for follow-up 2 to 4 weeks after discharge. In 46.4% of the patients treated with nonclindamycin regimens, the masses were decreased in size or absent, whereas 86% of clindamycin-treated patients showed a similar response (4). The excellent results reported by Hemsell et al. (80), Reed et al. (6), and McNeeley et al (7) provide additional evidence that using an agent effective against the Gram-negative anaerobic rods such as *B. fragilis, P. bivia,* and *P. disiens* enhances the clinical response to antimicrobial therapy.

Antibiotic Regimen	No. with Reduction of TOAs Size at Hospital Discharge (%)	No. with Further Reduction of TOAs Size at 2-4 Wk Postdischarge (%)
Antimicrobial regimens that included clindamycin	43/63 (68.3)	43/50 (86)
Antimicrobial regimens that excluded clindamycin	38/104 (36.5)	39/84 (46.4)

TOA, tuboovarian abscess.
Source: From Landers DV, Sweet RL. Tubo-ovarian abscess: contemporary approach to management. Rev Infect Dis 1983;5(Suppl):S876, with permission.

TABLE 8.13. COMPARISON OF CLINDAMYCIN-CONTAINING REGIMENS AND NONCLINDAMYCIN REGIMENS IN THE TREATMENT OF TOAS

The abscess is a unique environment. It is characterized by a low level of oxygen tension, and this low redox potential allows anaerobes to proliferate, which leads to tissue destruction and circulatory compromise, thus preventing many antibiotics from reaching the area. The combination of these forces and the poor phagocytosis by neutrophils in this environment are all important factors in the resistance of these infections to antimicrobial therapy. There are 10^7 to 10^9 bacteria per milliliter in an abscess. Thus, an inoculum effect can occur in which the laboratory standard of 10^5 organisms is sensitive to an antibiotic, but the tremendous numbers of organisms in the abscess are resistant. In addition, the high levels of enzymes produced by bacteria within the abscess aid in the destruction of many antibiotics such as penicillin, ampicillin, first-generation cephalosporins, ticarcillin, carbenicillin, and chloramphenicol. Many anaerobic bacteria, including *B. fragilis,* are often resistant to the penicillins and many cephalosporins. Included in these are the newly recognized strains, *P. disiens* and *P. bivia,* which are particularly prevalent in the female genital tract (80). The role of *B. fragilis* as an important pathogen in these infections is evident, based on recovery of this organism from abscess aspirates (4,52), serologic studies demonstrating an antigenic response in patients with abscesses (81), and experimental work in animals showing that *B. fragilis* promotes abscess formation (82).

As research continues to reveal the characteristics of clindamycin and other antibiotics, such as cefoxitin, metronidazole, and third-generation cephalosporins, which are active against these resistant Gram-negative anaerobes, we have an explanation for the improved response of TOAs to some antimicrobial treatment regimens. The extracellular antimicrobial activity of clindamycin may further explain the favorable results with this agent, but in addition, this agent may reach particularly high concentrations within the abscesses as a result of active transport into the abscess by polymorphonuclear leukocytes (83,84). Furthermore, in an animal model, clindamycin has been shown to enter infected encapsulated subcutaneous abscesses in mice in a higher concentration (43% to 63% of peak serum levels) than other antimicrobial agents, including metronidazole, cefoxitin, and moxalactam (85). However, these other antimicrobials did enter the abscesses in significant amounts. When the activity of ten antimicrobial agents was measured in these subcutaneous abscesses by reduction in bacterial counts, it was found that the most active

antimicrobials, in order of decreasing activity, were metronidazole, clindamycin, moxalactam, and cefoxitin (86).

The introduction of newer blactam agents offers additional treatment options. However, the *in vivo* ability of the extended-spectrum penicillins, piperacillin and mezlocillin, other third-generation cephalosporins, or the b-lactamase inhibition combinations to penetrate into abscesses and to reduce bacterial counts in abscesses has not been extensively studied. These agents also have not been widely studied in clinical practice.

We consider the combination of metronidazole or clindamycin with an aminoglycoside to be the most effective regimen available for the treatment of TOAs. The recent pattern of increased resistance by the *B. fragilis* group to clindamycin has led many clinicians to prefer metronidazole. In addition, many add ampicillin to their regimen for TOAs (7). Cefoxitin or possibly cefotetan-doxycycline is active against anaerobes including *B. fragilis, P. bivia,* and *P. disiens* and has generally provided comparative results versus a clindamycin or metronidazole regimen (6). The major disadvantage of this approach is the lack of an oral form of cefoxitin or cefotetan for continued therapy after discontinuation of parenteral therapy.

Surgical Management of TOA

In the preantibiotic era, the treatment of pelvic infections consisted only of bed rest, fluids, and heat. The semi-Fowler position was encouraged in hopes that purulent material would collect via gravity in the region of the cul-de-sac and would be accessible to colpotomy drainage. The first surgical drainage of a pelvic abscess was performed in the 1800s (27). This remained the only available alternative until the mid twentieth century, with the advent of antimicrobial preparations beginning with sulfa drugs and eventually penicillin. Surgical removal of infected pelvic organs remained a predominant mode of therapy, in spite of the addition of antibiotics to the armamentarium. In 1959, Collins and Jansen (87) summarized the treatment of pelvic abscesses in this way:

> In the therapy of acute pelvic infections, one operates immediately in cases of ruptured abscesses or abscesses pointing into the cul-de-sac or in the region of Poupart's ligament. Otherwise, medical therapy is employed. Failure to respond to these measures is a definite indication for surgery.

They went on to suggest that most pelvic abscesses eventually require surgical drainage or removal, but if possible, delaying the surgery until the infection had “cooled” was preferable (87). Recently, with the improvement in available antibiotics and the enhanced concern about infertility, an increasing number of investigators, as discussed earlier, have encouraged conservative management of the unruptured TOA (4,6,28,29).

The approach we currently use in the management of suspected TOAs is outlined in the algorithm in Fig. 8.6. If a ruptured TOA is suspected, the patient is stabilized, antibiotics are begun, and immediate surgical intervention is undertaken. The only other indication for immediate surgery is when the diagnosis is in question and there is the strong possibility of a surgical emergency. Otherwise, the patient begins

intravenous antibiotics that include an agent effective against resistant Gram-negative anaerobes such as *B. fragilis* and *P. bivia.* If, despite appropriate antimicrobial therapy, the patient does not begin to demonstrate evidence of response in a reasonable amount of time (e.g., 48 to 72 hours), we would then proceed with surgical intervention. This does not mean complete cure, but evidence of a response such as decreased temperature, decreased WBC count, or subjective improvement in the patient's symptoms. During the initial antibiotic therapy, the clinician must be aware of the fact that the abscess may rupture and become a surgical emergency. Once the decision to operate has been made, there should be no delay. Each case must be individualized; in young, nulliparous patients, an additional 24 to 48 hours is often allowed in hopes that they will begin to respond.

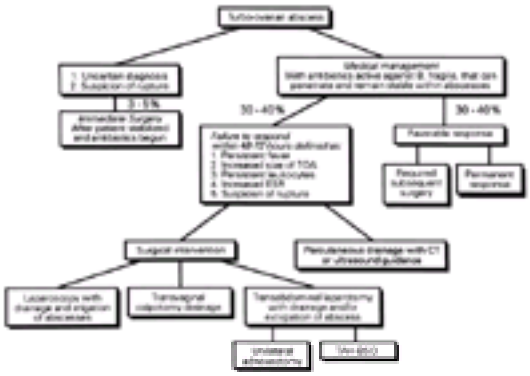

FIGURE 8.6. Algorithm for the management of tuboovarian abscesses.

A number of factors seem to have some predictive value in determining which patients are more likely to fail antibiotic therapy alone. Ginsberg et al. (29) noted that adnexal masses larger than 8 cm and bilateral adnexal involvement are predictive of failure to respond to medical therapy. Surprisingly, they noted that the presence of fever, the degree of leukocytosis, or the past history of PID was of no predictive value. Reed et al. (6) demonstrated that response to antimicrobial therapy was inversely proportional to size of the abscess (Fig. 8.7).

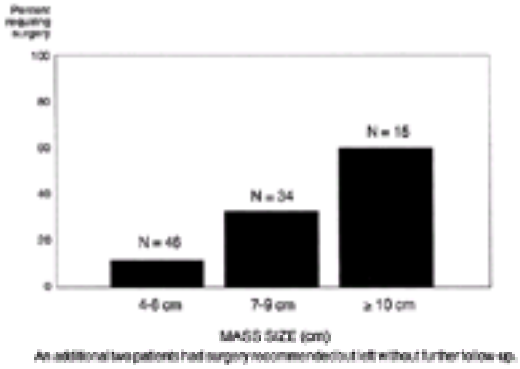

FIGURE 8.7. Size of tuboovarian abscess as a predictor of clinical response to

antimicrobial therapy alone.

The Ruptured TOA

One of the most serious complications associated with TOAs is intraabdominal rupture, a surgical emergency for which the mortality rate is rapidly increased by unnecessary delay. In 1964, Pedowitz and Bloomfield (23) reported 143 cases of ruptured adnexal abscesses. Sixteen of these cases were treated before 1947, with a 100% mortality rate. From 1947 to 1959, 127 cases were treated with a more aggressive surgical approach combined with available medical adjuvants, and the mortality was 3.1%. Pedowitz and Bloomfield (23) also reported that there were 235 published cases after 1945 treated by centers using an operative approach, and in analyzing the 14 deaths that occurred, they felt that 10 may have been prevented. Physician delay in establishing the diagnosis was cited as the most common cause of preventable death. Collins and Jansen (87) similarly reported an 85% mortality rate before 1952, but after adopting an aggressive surgical approach in addition to antibiotic therapy from 1953 to 1959, they reported 58 patients with ruptured TOAs and only one death. They estimated an expected recovery rate of 10% to 15% using a medical regimen and an 85% to 90% recovery rate with the surgical approach (87). Subsequent investigators have continued to show improved survival with aggressive surgical management of ruptured TOAs. In 1969, Mickal and Sellmann (31) reported an 11.1% mortality rate from 1951 to 1959 and 3.7% from 1959 to 1966. On the other hand, Rivlin and Hunt (88), in 1977, reported 71% mortality in 113 patients with ruptured TOAs. The major difference in this series was the extent of surgery performed at the time of laparotomy. In this series (88), hysterectomy was performed in only 3% of the patients, with hormonal and menstrual function being retained in 73.5%. This was a surprise, considering the 70% hysterectomy rate reported by Pedowitz and Bloomfield (23), as well as the 80% rate in the Mickal and Sellmann series (31). In addition, only 17.5% of patients in the Rivlin and Hunt (88) report required further surgery at a later date in the 1- to 5-year follow-up period. Landers and Sweet (4) recently reported four patients with ruptured TOAs who underwent unilateral adnexectomy, and none required further surgery in the 2- to 10-year follow-up. One patient carried a subsequent intrauterine pregnancy to term. It appears that when aggressive surgical intervention is combined with appropriate antibiotic therapy in the treatment of ruptured unilateral TOAs, a conservative surgical approach using unilateral adnexectomy and aimed at preserving hormonal and reproductive function can be safely employed.

Surgical Approach to Unruptured TOAs

No general consensus exists as to the appropriate surgical approach for the unruptured TOA. The techniques that have been used include extraperitoneal drainage, posterior colpotomy drainage, transabdominal drainage, unilateral adnexectomy, and total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Extraperitoneal drainage of TOAs was used in the past to drain abscesses accessible to an incision just above the Poupart ligament. This procedure unfortunately requires adherence of the parietal and visceral peritoneum. We will not

describe this procedure in detail, because its place in the treatment of TOAs is very limited and can probably be replaced with better results by imaging directed percutaneous or laparoscopic directed drainage.

Drainage of TOAs through a posterior colpotomy has been used for many years. This procedure is an effective mode of treatment when combined with antimicrobial therapy and restricted to patients with fluctuant abscesses in the midline, which dissect the rectovaginal septum and are firmly attached to the parietal peritoneum. These requirements markedly reduce the number of TOAs that can be safely drained by this procedure. The morbidity of colpotomy is significantly greater if these requirements are not met. Rubenstein et al. (89) reported 65 patients with pelvic abscesses that were drained by colpotomy or rectal incision. About one third of these patients required a subsequent major operation because of residual pain or infection (89). In 1982, Rivlin et al. (90) reported a combined series of 348 cases of colpotomy drainage, resulting in 23 cases of diffuse peritoneal sepsis (6.5%). Of these 23 cases, there were six (26%) deaths. In 1983, Rivlin (91) reported 59 patients treated over 20 years with colpotomy drainage in which there were two deaths, both related to diffuse peritonitis after septic abortion. Further surgery during the same admission was performed in 13 instances; additional surgery at a later date in 11 patients. Fourteen (58%) of these 24 second surgical procedures were performed as emergency operations (91). Colpotomy drainage, if appropriate, should be performed under general anesthesia, with the patient in the dorsal lithotomy position. The bladder is emptied, and an examination under anesthesia is performed to ensure that the abscess is adherent (i.e., that it cannot be moved out of the cul-de-sac) and appropriate for colpotomy drainage. The vagina is then prepared with Betadine solution and a tenaculum is used on the posterior lip of the cervix for countertraction. The vaginal mucosa is incised in a transverse manner at the junction of the posterior vaginal fornix with the cervix. The abscess cavity is entered with a Kelly clamp, which is then opened to enlarge the incision. Appropriate cultures are obtained, and the abscess cavity is subsequently explored, usually with the surgeon's finger to break down any adhesions or loculation within the abscess cavity. The use of intraoperative real-time sonography greatly facilitates drainage of the entire abscess, particularly when it is multiloculated. A closed-suction catheter is inserted into the cavity for drainage. This catheter is removed 48 to 72 hours after drainage has stopped. Colpotomy drainage can be a useful adjuvant in the treatment of those unilocular TOAs that fit the specific requirements for vaginal drainage and that are resistant to treatment with antibiotics alone. There still exists some danger of diffuse peritoneal sepsis and death, but this can be minimized by carefully selecting the patients who would benefit from this form of therapy.

Vaginal colpotomy drainage is rarely performed today. It was designed and was appropriate for use in the preantibiotic era, when extraperitoneal drainage of abscesses was a paramount need. Without concurrent antibiotic therapy, a transabdominal approach to an acute abscess would most likely result in peritonitis and high mortality rates. Our lack of enthusiasm for vaginal colpotomy drainage is based on the following: (a) There is a high rate of complications and subsequently more definitive surgery after colpotomy drainage (89,90 and 91); (b) most TOAs do not meet the requisite requirements for the vaginal approach (i.e., midline mass that adheres to pelvic peritoneum and dissects the upper one third of the rectovaginal septum; and (c) with the high incidence of unilateral abscesses being reported, it is our belief that unilateral adnexectomy with extirpation of infected tissue offers a better chance for preservation of future fertility or hormonal production from the contralateral adnexa. Similarly, ultrasound, CT scan, or laparoscopy-directed

drainage is a preferred alternative.

Conservative Surgery Versus Total Hysterectomy with Bilateral Adnexectomy

Some controversy remains concerning the extent of surgery that is appropriate for the patient requiring surgical intervention in the treatment of a TOA. A number of investigators have advocated the complete removal of all reproductive organs by total abdominal hysterectomy with bilateral salpingo-oophorectomy (23,24,79,87). This approach was stimulated by the report of Pedowitz and Bloomfield (23) that in patients with only unilateral TOAs grossly, one third had microscopic abscesses on the contralateral ovary. The alternative approach is a unilateral salpingo-oophorectomy for unilateral TOAs, with bilateral salpingo-oophorectomy limited to patients with bilateral disease. Although it is true that complete removal of reproductive organs is most often curative, the more conservative unilateral adnexectomy offers the advantage of a hope for future fertility, maintenance of hormonal and menstrual function, and the avoidance of the physiologic and psychologic effects of hysterectomy and gonadectomy. The major question involved is whether these benefits outweigh the risk of requiring further surgical therapy. As antibiotic regimens continue to improve and more data accumulate on the patients treated with conservative surgery, it appears that such a conservative approach is appropriate.

Several investigators have reported results of conservative surgical management of patients with unilateral TOAs (4,23,26,29,30,52,71,88). These data, summarized in Table 8.14, indicate that approximately 17% of patients treated with unilateral adnexectomy will require additional surgery at a later date and that approximately 14% will have a subsequent intrauterine pregnancy. Unfortunately, the data on conservative surgical treatment of TOAs are retrospective and suffer from poor long-term follow-up. Included in this group is the unique series of Rivlin and Hunt (88). They combined conservative surgery with intraoperative and postoperative antibiotic peritoneal lavage for the treatment of 113 patients with ruptured TOAs. They found that only four patients (3%) required hysterectomy initially. In the 83 patients treated with adnexal procedures (unilateral or bilateral) without removal of the uterus, 16 (19%) required further surgical intervention. In the recent series by Landers and Sweet (4), 19 patients were treated with unilateral adnexectomy, and only 2 required subsequent surgery, whereas three had subsequent pregnancies. Thus, it appears that although there is a risk that further surgery will be required, the conservative surgical approach does offer the patient with a TOA who fails initial antibiotic therapy another alternative to permanent sterilization and castration. Perhaps patients with unilateral TOAs that do respond to antibiotics initially but have persistence of their mass could benefit from unilateral adnexectomy in terms of future fertility and flare-ups. There is likely to be a continued demand for the conservative surgical approach, particularly as such techniques as *in vivo* fertilization and donor embryo transplantation become available. Conservative surgery, in which the uterus is left in place and any healthy ovarian tissue is preserved, may be an acceptable procedure in selected cases in which future fertility is desired. Drainage guided by ultrasound, CT scan, or laparoscopy probably accomplishes the same goals.

Study	No. Treated with Unilateral Adnexectomy	No. Requiring Subsequent Surgery (%)	No. with Subsequent Pregnancy (%)
Pedowitz and Bloomfield [23]	14	6 (43)	NS
Landers and Sweet [4]	19	2 (10.5)	3 (15.8)
Hager [26]	6	0 (0)	4 (80)*
Ginsberg et al. [29]	5	1 (20)	NS
Mickal and Sellmann [31]	8	1 (12.5)	NS
Goide et al. [52]	12	0 (0)	1 (8.3)
Manara [71]	10	0 (0)	NS
Rivlin and Hunt [88]	27	7 (26)	1 (3.7)
Total	101	17 (16.8)	9/64 (14.1)

*Only five of the six patients treated with unilateral adnexectomy attempted to conceive.

TABLE 8.14. SUMMARY OF TREATMENT WITH UNILATERAL ADNEXECTOMY

Fertility After TOAs

The preservation of reproductive organs in the management of TOAs is in no way a guarantee of future fertility, particularly in patients who may well have tubal damage from previous episodes of upper genital tract infection. Although several investigators have reported the incidence of pregnancy after TOAs, the follow-up was very limited, leaving it impossible to assess the number of patients attempting to conceive and their success rate (4,26,28,29,52,88,90). The pregnancy rate has been reported to range from 9.5% to 15% after conservative medical management (4,26,28,29,71,80), 3.7% to 16% after unilateral adnexal procedures with preoperative antibiotics (4,29,52,88), and 10% to 15% after antibiotics plus colpotomy drainage (88,90). Hager (26) recently published a series in which 50 patients treated for TOAs were evaluated. A total of 11 of these patients had reproductive potential after treatment, but only 8 attempted to conceive. Four of the eight (50%) conceived a total of five intrauterine pregnancies. There were no ectopic pregnancies. Included in this group were five patients who underwent a unilateral salpingo-oophorectomy and attempted to conceive, of which four were successful (80%). Acknowledging that these numbers are very small, we must recognize that we may be dramatically underestimating reproductive potential after TOAs, unless we consider the number of patients attempting to conceive after conservative medical or surgical management. Furthermore, very few data have been published on patients treated vigorously with antibiotics such as clindamycin, metronidazole, or cefoxitin, which can penetrate abscesses. More investigation is needed to elucidate the role of unilateral adnexectomy in the enhancement of future fertility after a unilateral TOA.

Newer Approaches to the Management of TOAs

Percutaneous Disease

Percutaneous drainage guided by CT or real-time ultrasound is commonly used in the management of intraabdominal abscesses, and more recently, pelvic abscesses. This technique has been reported to be successful in 75% to 89% of intraabdominal abscesses (92,93,94 and 95). Most abscesses successfully drained by this technique have been unilocular abscesses. Mandel et al. (92), however, have performed

percutaneous drainage on multilocular abscesses. They report success with placement of more than one drainage tube for multilocular abscesses (92). Interest in less invasive techniques in an attempt to decrease morbidity, decrease hospital stay, and decrease cost has led to increasing interest in interventional radiologic approaches to drainage of pelvic abscesses. Worthen and Gunning (96) demonstrated excellent results, wherein they had a 95% success rate with transabdominal ultrasonographically guided percutaneous drainage of pelvic abscesses and a 77% rate with drainage of larger abscesses with indwelling catheters. Of note was their difficulty draining abscesses in the retrouterine location or where bowel or vascular structures intervened. Tyrrel et al. (97) used CT-guided drainage in eight patients with TOAs and reported success in seven (87.5%). Again there were technical difficulties accessing retrouterine abscess that were addressed by using a transgluteal approach (20). However, the increased cost of CT relative to ultrasound and the discomfort associated with the transgluteal approach have limited the usefulness of CT-directed drainage of TOAs and pelvic abscesses (20).

Subsequently, attention was turned to the use of endovaginal ultrasound guidance and transvaginal drainage of pelvic abscesses (20,98,99,100,101,102,103,104 and 105). Endovaginal ultrasound-directed transvaginal drainage of pelvic abscesses has been successful in approximately 85% of the cases (20,98,99,100,101,102,103,104 and 105). More recently, transrectal ultrasonographically guided drainage of gynecologic pelvic abscesses has been advocated (21,106,107,108,109,110,111 and 112). Nelson et al. (21) reported excellent results using this approach for retrouterine abscesses. These authors successfully drained 14 (93%) of 15 pelvic abscesses.

In addition to localization and percutaneous insertion of catheters for drainage of abscesses, the CT scan and ultrasound are also used to follow the response of these abscesses to the drainage technique. Second scans are generally performed within 48 hours after drainage to evaluate response. These catheters can also be used for irrigation of the abscess cavities, as well as injections of contrast material to ensure reduction of cavity size on repeated scans. The evaluation of this technique in the treatment of TOAs in significant numbers has yet to be reported.

Laparoscopic Drainage

The role of laparoscopy in the diagnosis and management of salpingitis has revolutionized current thinking on the etiology and pathogenesis of the disease process. The laparoscope may also prove extremely useful in the management of TOAs. This technique offers the advantage of direct visualization of the abscess being drained, as well as confirmation of the diagnosis. The laparoscopic approach is associated with less morbidity and cost than laparotomy drainage or extirpation of abscesses. Laparoscopic surgical management for adnexal abscesses was first proposed by Dellenbach et al. (113) in 1972. Subsequently, several investigators have published results confirming the effectiveness of this approach (114,115,116,117 and 118). Adducci (114) reported his experience with colpotomy drainage during laparoscopy of nine patients with PID-associated pelvic abscesses. All nine patients responded well to this approach. Henry-Souchet et al. (115) have also reported excellent results with laparoscopic treatment of TOAs. They noted complete and rapid recovery in 45 (90%) of 50 cases. Among the 32 recent TOAs, 31 (97%) responded versus 14 (78%) of 18 long-standing abscesses. However, caution is necessary because it appears that what were called *recent TOAs* may well have been acute PID with early adhesive disease. Reich and McGlynn (116)

reported in a series of 25 patients with TOA and/or pelvic abscess that 24 (96%) responded to laparoscopic drainage, whereas only 1 (4%) failed and required a total abdominal hysterectomy and bilateral salpingo-oophorectomy 1 month later. In addition, in the five women in their series who underwent second-look laparoscopy, only minimal adhesions were seen (116). More recently, Raiga et al. (118) reported excellent results with this approach. These authors treated 39 patients for adnexal abscesses with laparoscopic drainage. All 39 patients had an immediate clinical response. In 35 patients, a second-look laparoscopy at 3 to 6 months was performed; lysis of adhesions was necessary in all 35, and a distal tuboplasty was performed in 17 patients (118). In follow-up, 12 (63%) of 19 patients not using any contraception obtained a spontaneous intrauterine pregnancy.

Although laparoscopically directed drainage of TOAs and pelvic abscesses appears to be a useful alternative, additional evaluation is required. To date, there has not been any prospective randomized controlled studies comparing laparoscopic draining with ultrasonographic/CT scan–directed percutaneous drainage or medical treatment alone. Of most importance is the need not only to assess early clinical response but also to determine long-term outcomes (e.g., fertility, ectopic pregnancy) between antimicrobial therapy alone and antimicrobial therapy in combination with drainage procedures.

Summary: Pelvic Abscess

TOAs remain a common sequelae of acute PID and are associated with significant reproductive morbidity. Patients with TOAs most commonly present with lower abdominal pain and one or more adnexal masses. Fever and leukocytosis may be absent. Ultrasound, CT scans, laparoscopy, or laparotomy may be necessary to confirm the diagnosis. TOAs may be unilateral or bilateral regardless of IUD usage. The microbiology of TOAs is polymicrobial with a preponderance of anaerobic organisms.

An initial conservative antimicrobial approach to the management of the unruptured TOA is appropriate if the antimicrobial agents used can penetrate abscesses, remain active within the abscess environment, and are active against the major pathogens in TOAs, including the resistant Gram-negative anaerobes such as *B. fragilis* and *P. bivia.* However, if the patient does not begin to show a response within a reasonable amount of time, i.e., 48 to 72 hours, surgical intervention should be undertaken. Suspicion of rupture should remain an indication for immediate surgery. Once surgery is undertaken, a conservative approach with unilateral adnexectomy for one-sided TOAs is appropriate if future fertility or hormone production is desired. The surgery may be difficult, requiring careful dissection and postoperative intraperitoneal drainage. Delayed primary closure can be used to decrease postoperative infectious complications. Percutaneous drainage guided by ultrasound or CT scan and laparoscopic drainage are increasingly used alternative approaches for patients not responding to antimicrobial therapy alone.

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9

HEPATITIS INFECTION

Acute viral hepatitis is a self-limiting infection that predominantly affects the liver, resulting in a necroinflammatory response (1). Hepatitis is one of the most common viral infections. Formerly, acute hepatitis was divided into two types based on clinical and epidemiologic characteristics: type A or infectious hepatitis and type B or serum hepatitis. Subsequently, five distinct hepatitis viruses have been identified: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis D or delta virus (HDV), hepatitis C virus (HCV), which is the cause of parenterally transmitted and community-acquired non-A, non-B hepatitis, and hepatitis E virus (HEV), an enterically transmitted epidemic non-A, non-B hepatitis. In Table 9.1, these distinct types of viral hepatitis and their characteristics are summarized. Despite the presence of multiple causative viruses, the clinical presentations of acute viral hepatitis are nearly identical. As a result, specific diagnosis of the etiologic agent requires serologic assays that are specific for each of the different viruses. The laboratory tests (serologic) used to differentiate the various types of acute hepatitis are listed in Table 9.2.

	A	B	C	D	E
Type Virus	RNA	DNA	RNA	RNA	RNA
Incubation	21 d (15–45)	70 d (30–180)	50 d (15–150)	?	40 d (15–60)
Cytotoxic	+	-	+	+	+
Acute disease	+++	+++	+	++	+++
Chronic carrier	-	+	+++	+	-
Associated with cirrhosis	-	+	+++	+	-
Associated with hepatocellular carcinoma	-	+	++	?	-
Perinatal transmission	-	+++	+	++	-
Vaccine	+	+	-	-	-
Passive immunity	+	+	-	-	-
Estimated annual cases in the United States	140,000 (125,000–200,000)	300,000 (140,000–320,000)	150,000 (25,000–180,000)	10,000 (6,000–13,000)	<100

TABLE 9.1. CHARACTERISTICS OF THE MAJOR TYPES OF VIRAL HEPATITIS

	Serologic Test for	
Viral Agent	Acute Infection	Chronic Carrier State
HAV	IgM HAV	None
HBV	HBsAg HBeAg IgM HBcAg	HBsAg
HCV	HCV antibody	Persistent biochemical evidence hepatic dysfunction
HDV	D antigen IgM HDV	D antigen IgG HDV
HEV	Viral particles in stool on electron microscopy Fluorescent antibody blocking assay IgM HEV	None

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBcAg, hepatitis B core antigen; IgM, immunoglobulin M; IgG, immunoglobulin G.

TABLE 9.2. SEROLOGIC TESTS FOR DIAGNOSIS OF VIRAL HEPATITIS

This discussion will emphasize the epidemiology, mode of transmission, and clinical aspects of these five forms of hepatitis. The effects of these viruses during pregnancy on the mother, fetus and neonate are reviewed. Clinically apparent icteric hepatitis is only one part of the disease spectrum and that “silent” infections (carrier state) may result in chronic and progressive disease in the mother and her offspring.

Additional viruses have recently been proposed as potential specific hepatitis viruses. These include hepatitis F virus (HFV), the hepatitis-related GB virus C (GBV-C), and hepatitis G virus (HGV) (1). HFV was recovered from the feces of a patient with hepatitis and subsequently transmitted to primates (2). This finding has not been subsequently confirmed, so the role of HFV in acute hepatitis remains unclear. The bloodborne hepatitis viruses GBV-C and HGV were discovered independently by two separate groups but are considered isolates of the same virus (3,4). However, a consensus has not yet occurred on the significance of GBV-C and HGV as hepatitis viruses (1). More recently, another potential hepatitis virus called TT virus (TTV) was identified from the serum of a patient with non–A-G posttransfusion hepatitis (5). Similarly, there remains uncertainty about its etiologic

role in acute viral hepatitis (1).

Various other viral agents also infect the liver, producing an acute viral hepatitis–like syndrome. However, these cases of hepatitis present as part of a more systemic clinical presentation. These agents include cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus, rubella virus, rubeola virus, Coxsackie B virus, adenovirus, and yellow fever virus.

Although acute viral hepatitis is a common infection and is a reportable disease in the United States, the true incidence of this disease is not known. From 1984 to 1994, the Centers for Disease Control and Prevention (CDC) estimated that in the United States, the number of annual acute infections of HAV was from 125,000 to 200,000; HBV, 140,000 to 320,000; HCV, 35,000 to 180,000; and HDV, 6,000 to 13,000. The CDC estimated that 84,000 to 134,000 of the HAV cases, 70,000 to 160,000 of HBV cases, and 25% to 30% of HCV were symptomatic infections. During this period, HAV accounted for 47% of acute hepatitis; HBV, 34%; HCV, 16%; and the remainder, 3%. The number of hepatitis A cases has been increasing, whereas that of hepatitis B (post–HBV vaccine) and that of hepatitis C (post–donor screening) have declined. The risk factors associated with acute hepatitis types A, B, and C are listed in Table 9.3. The risk factors for HBV and HCV are similar, reflecting their similar modes of transmission (largely parenteral and sexual), whereas those for HAV differ, reflecting the fecal-oral transmission route (1).

Hepatitis A (% of Total)	Hepatitis B (% of Total)	Hepatitis C (% of Total)
Personal contact (24)	Heterosexual (41)	Injection drug use (43)
Daycare associated (15.1)	Injection drug use (15)	Sexual contact (15)
Foreign travel (5.5)	Homosexual contact (9)	Other (14)
Outbreak associated (4.7)	Household (2)	Past drug use (31)
Male homosexual (3.8)	Health care worker (1)	Cocaine snorting (5)
Injection drug use (2.4)	Other (1)	Occupation (4)
Unknown (44.5)	Unknown (31)	Transfusion (4)*
		Household (3)

*Since 1995, transfusion-associated hepatitis C virus infection has virtually disappeared in the United States.
Source: From Kawai H, Feinstone SM. Acute viral hepatitis. In: Mandel GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. New York: Churchill Livingstone, 2000:1279–1297, with permission.

TABLE 9.3. RISK FACTORS ASSOCIATED WITH ACUTE VIRAL HEPATITIS A, B, AND C, UNITED STATES

Despite its common occurrence and often benign course, acute viral hepatitis is a serious disease. The estimated mortality rate of viral hepatitis associated with clinical jaundice is 1% (1). In general, the frequency of fulminant hepatitis and the mortality rates are dependent on the age of infected persons and the causative agent of the hepatitis (1). The mortality rate is higher in young adult patients. Fulminant hepatitis occurs more commonly with hepatitis type B and type D than with other types of hepatitis, with mortality rates ranging from 2% to 20% in reported outbreaks of delta hepatitis (6,7). In addition, unique findings with HEV include an increased incidence of fulminant hepatitis and a high mortality rate (approximately 10%), which occur in pregnant women, particularly in the third trimester of pregnancy (8). Although an

exact incidence of mortality with acute HCV infection has not been reported, fatal cases do occur. HDV is associated with severe cases of HBV disease and is responsible for up to one third of the cases of fulminant hepatitis (9). Of greater concern than the morbidity and mortality associated with acute hepatitis is the development of a chronic state with hepatitis types B, C, and D, which can lead to significant sequelae such as chronic liver disease, cirrhosis, hepatocellular carcinoma, and nonhepatic diseases including polyarteritis nodosa, cryoglobulinemia, glomerulonephritis, and aplastic anemia (1,10,11). Chronic viral hepatitis is the second most common (after alcohol) cause of cirrhosis in the United States and western Europe (1). Chronic hepatitis types B, C, and D are common causes of end-stage liver disease, for which liver transplantation is performed (1). In the United States, HCV infection is the most common indication for liver transplantation (12,13). Worldwide, chronic HBV infection is the most important cause of cirrhosis and a major cause of cancer mortality due to hepatocellular carcinoma (14). As reported by Beasley et al. (11), on a worldwide scale, HBV may be the single major cause of mortality secondary to cancer. They estimated that approximately 5% of the world's population has chronic HBV infection and up to 40% of these chronic carriers will ultimately develop hepatocellular carcinoma. Similarly, chronic HCV infection is associated with an increased risk of hepatocellular carcinoma (15,16,17 and 18).

CLINICAL MANIFESTATIONS ACUTE VIRAL HEPATITIS

Acute viral hepatitis presents with a wide spectrum of findings, ranging from asymptomatic disease to fulminant hepatitis. No clinical features are specific enough to clearly differentiate among the various types of hepatitis. Although certain epidemiologic patterns of transmission may point to a particular hepatitis agent (Table 9.4), confirmation of etiology requires serologic studies.

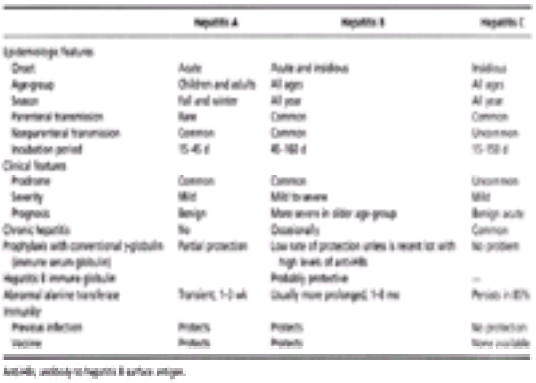


TABLE 9.4. CLINICAL AND EPIDEMIOLOGIC FEATURES OF ACUTE VIRAL HEPATITIS

The initial symptoms associated with the preicteric phase of acute hepatitis are nonspecific; malaise and weakness are the earliest and most common (95%) symptoms, followed rapidly by anorexia, nausea, vomiting, and mild, dull, right upper quadrant pain (1). This preicteric phase typically lasts 3 to 10 days. The icteric phase

commences with onset of jaundice or dark urine or both. However, clinically evident icterus is present in only 20% to 50% of acute viral hepatitis infections (1). Approximately, 5% to 15% of patients with acute hepatitis present with a “serum sickness–like syndrome” during the preicteric phase (19,20). This syndrome is characterized by a triad of symptoms: fever, rash (urticarial), and arthritis (polyarticular and migratory) (1). With the onset of jaundice, the “serum sickness–like syndrome” rapidly resolves. Other immune complex–mediated diseases are associated with acute viral hepatitis. These include polyarteritis nodosa (HBV), glomerulonephritis (HBV and HCV), and mixed cryoglobulinemia (HBV and HCV) (1).

The most serious manifestation of viral hepatis is fulminant viral hepatitis, which is defined as severe acute liver failure with hepatic encephalopathy that occurs 8 or less weeks after the onset of jaundice (21). HBV is responsible for 30% to 60% of these cases, and 30% to 40% of such patients are coinfected with delta virus (1). On the other hand, HAV infection is an uncommon cause, with less than 0.1% of acute hepatitis A cases progressing to liver failure, and HCV alone has not been associated with acute fulminant hepatitis (1). In addition, some evidence suggests that HGV is associated with fulminant hepatitis (22,23 and 24). However, as discussed previously, no consensus exists on whether HGV is a hepatitis virus (1).

Physical examination in acute viral hepatitis reveals few findings. When the bilirubin level exceeds 2.5 to 3.0 mg/dL, icterus can be detected. Other findings on the skin include vascular spiders and when severe pruritus exists, excoriations. On abdominal examination, the liver is slightly enlarged and tender. In patients with serum sickness–like syndrome, an urticarial rash and erythematous warm and tender joints are present. With fulminant hepatitis, patients demonstrate signs of hepatic encephalopathy, including lethargy, somnolence, confusion, stupor, and ultimately full coma and asterixis (asynchronous flapping of dorsiflexed hands).

Laboratory findings associated with acute viral hepatitis are fairly specific. The most characteristic laboratory findings include dramatic elevations in aspartate aminotransferase and alanine aminotransferase (ALT). In contradistinction, alkaline phosphatase and lactic dehydrogenase levels are only mildly elevated. Bilirubin level, both direct and indirect in an equal ratio, is elevated in icteric hepatitis. In nonfulminant cases of acute viral hepatitis, the prothrombin time is within the normal reference range. A prolonged prothrombin time is a serious sign and raises concern that more severe liver necrosis, progressing to fulminant hepatic failure, may occur.

HEPATITIS A

Epidemiology

Hepatitis A is caused by infection with HAV, a 27-nm RNA virus that is a member of the Picornaviridae family and may be classified as an enterovirus (1,25,26,27 and 28). Hepatitis A is usually a mild self-limited disease without any chronic sequelae. Infection may be asymptomatic or may result in acute hepatitis (27,28). Fulminant hepatitis is rare (27). It is estimated that hepatitis A is responsible for 30% to 35% of hepatitis cases in the United States (26,29). In 1998, there were 23,229 cases of hepatitis A reported in the United States (30). The CDC estimates (after adjusting for underreporting and asymptomatic infection) that there were 90,000 cases of symptomatic hepatitis A and 180,000 persons had HAV infection (30). The mortality

rate of hepatitis A is low (about 2 per 1,000 icteric cases) and an estimated 100 persons die each year in the United States because of acute liver failure due to fulminant hepatitis A (1,27,28). However, adults older than 50 years and persons with chronic liver disease are at increased risk for fulminant hepatitis A (27,31). Mild and clinically unrecognized infections with HAV commonly occur in childhood (90% in those younger than 5 years) and account for the high incidence of immunoglobulin G class antibody to HAV (IgG anti-HAV) in adult populations, a finding reflected in the adequate antibodies present in normal immune serum globulin. The prevalence of previous HAV infection in the United States has been estimated to range from 33% to 38% (26,31).

Transmission

HAV is transmitted predominantly by way of the fecal-oral route. HAV is highly contagious and can spread rapidly from person to person. HAV has been demonstrated to be spread by (a) contaminated water, milk, or food; (b) breakdown in sanitary conditions after floods or other natural disasters; (c) ingestion of raw or undercooked shellfish (e.g., oysters, clams, and mussels) from contaminated water; (d) travel to areas with poor hygienic conditions where hepatitis A is endemic; (e) exposure to children in day care centers; and (f) exposure to institutionalized individuals (1,27). In addition to the predominant route of fecal-oral transmission, HAV is transmitted by other routes such as intravenous drug abuse and sexual contact, particularly among homosexual men in whom HAV infection correlates with the number of sex partners and frequency of oral-anal contact (32,33,34 and 35). Perinatal transmission of HAV is very rare. Watson et al. (36) reported a case in which vertical transmission of HAV apparently occurred as a result of a placental abruption. The infant was seropositive for immunoglobulin M class antibody to HAV (IgM anti-HAV) and the virus spread to nursery staff and other newborns. Persons in the United States who are at high risk for hepatitis A are those who have recently traveled to or immigrated from developing countries where hepatitis A is an endemic disease.

Diagnosis

Acute viral hepatitis is a clinical syndrome that can be divided into four stages: (a) incubation period; (b) preicteric phase; (c) icteric phase; and (d) convalescence. The clinical manifestations of viral hepatitis are usually so characteristic that diagnosis is reasonably straightforward (see previous discussion under Clinical Manifestations of Acute Hepatitis). The comparative epidemiologic and clinical features of hepatitis A, B, and C are shown in Table 9.4. The incubation period for hepatitis A ranges from 2 to 6 weeks (mean, 28 to 30 days). HAV excretion peaks late in the incubation period and early in the preicteric phase, with the highest concentration in fecal material.

There are no reliable methods to differentiate clinically among the types of acute viral hepatitis. Thus, once a diagnosis of acute viral hepatitis has been entertained, identification of the responsible viral agent requires use of serologic markers (Table 9.2). The serologic course of HAV infection is shown in Fig. 9.1. Anti-HAV is present in the serum by the time of onset of clinical symptoms. The presence of IgM anti-HAV in a patient with clinical symptoms or enzyme evidence of acute viral hepatitis is diagnostic of HAV infection. After 3 to 12 months, IgM anti-HAV disappears and IgG anti-HAV persists to provide lifelong immunity.

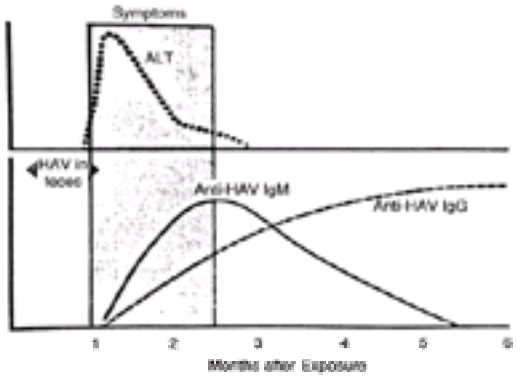


FIGURE 9.1. Serologic pattern with hepatitis A.

Pregnancy-Associated Hepatitis A

It is estimated that hepatitis A occurs in approximately 1 per 1,000 pregnancies. There is no evidence that pregnant women are more susceptible to HAV, and the course of hepatitis A is similar in pregnant and nonpregnant women. Usually, hepatitis A produces no adverse effect on the fetus; neither perinatal transmission (exception one case report [36]) nor a chronic carrier state in the newborn occurs. No teratogenic effect of HAV has been noted. Transmission to the neonate from a mother acutely infected with HAV via the fecal-oral route is possible during delivery and postpartum. It appears reasonable to administer immunoglobulin (Ig) to infants born to mothers who develop acute hepatitis A during the third trimester (or just before delivery) (26). Whether such an approach is cost effective has not been demonstrated.

Treatment

There is no specific therapy for acute hepatitis A. Thus, the management of patients with hepatitis A consists primarily of supportive measures. Most of the patients with hepatitis A (including pregnant patients) can be managed on an outpatient basis. In general, patients require increased bed rest, a diet high in protein, and avoidance (if possible) of drugs that are hepatotoxic or metabolized by the liver (1,27,29). In most patients, hepatitis A is mild and is usually a self-limited infection. Indications for hospitalization of patients with hepatitis A include (a) intravenous alimentation in patients unable to tolerate oral intake; (b) severe anemia; (c) diabetes; (d) a prolonged prothrombin time; (e) low serum albumin level; and (f) bilirubin level of more than or equal to 15 mg/100 mL. Patients with evidence of fulminant hepatitis, coagulopathy, or encephalopathy require treatment in an intensive care setting (37).

Patients usually recover from acute hepatitis A within 4 to 6 weeks. Hepatitis A does not progress to chronic hepatitis and there is no HAV carrier state. The mortality rate for hepatitis A is low, ranging from 0.1% to 0.2% (29).

Prevention

Although no specific antiviral agents are available to treat hepatitis A, effective preventative measures of HAV transmission exist. Two types of products are available for prevention of hepatitis A: hepatitis A vaccine and Ig. Passive immunization with pooled Ig (g-globulin) has been used to prevent transmission or to ameliorate symptoms of acute hepatitis A since the 1940s (38). Before the licensing of hepatitis A vaccines, pooled Ig was the mainstay of hepatitis A immunoprophylaxis (39). Post–vaccine availability, Ig still plays an important role in hepatitis A prophylaxis. It is useful for preexposure prevention of hepatitis A in travelers to endemic areas where the 2 weeks required for vaccine effectiveness is not available. In addition, Ig remains useful in postexposure prophylaxis for common source or family outbreaks (39). Ig is recommended for postexposure prophylaxis and for unvaccinated persons expecting to be in a high-risk situation in less than 2 weeks. Ig is also recommended for preexposure prophylaxis for persons allergic to one of the vaccine components and for children younger than 2 years (vaccine not approved) (39). Postexposure prophylaxis is recommended in persons known to have been exposed less than 2 weeks before immunization. The usual dose of Ig is a single intramuscular injection of 0.02 mL per kilogram of body weight, which will provide protection for up to 3 months. If exposure for 3 to 6 months is expected a single injection of 0.06 mL/kg should be provided. For longer exposure, 0.06 mL of Ig per kilogram of body weight is repeated every 5 months (39). Ig recommendations for prophylaxis and the recommended doses for Ig are provided in Table 9.5.

Clinical Situation	Recommended Dose
Recent close personal (household) or sexual contact with person who has acute hepatitis A	Immune globulin, 0.02 mL/kg i.m. within 2 wk of exposure*
Individuals who plan to travel to areas of the world where hepatitis A endemic (North Africa, Central and South America, and Asia)	
Duration travel, <2 mo	Immune globulin, 0.02 mL/kg i.m.
Extended travel	Immune globulin, 0.06 mL/kg i.m. administered every 5 mo
Infants of mothers who may be infectious at or soon after delivery	Immune globulin, 0.02 mL/kg i.m.

*Candidates for new inactivated hepatitis A vaccine once it becomes clinically available.

TABLE 9.5. RECOMMENDED DOSE OF g-GLOBULIN FOR PREVENTION OF HEPATITIS A

Active immunization (vaccine) is also now possible against hepatitis A. In the United States, two HAV formalin-inactivated hepatitis A vaccines are currently approved and available. A recombinant vaccine based on VPA, the major surface polypeptide of hepatitis A, is available for clinical use in Europe. Inactivated hepatitis A vaccines, available in the United States since 1995, are administered as a two-dose series in which a booster dose is given 6 to 12 months after the initial dose. The vaccines are safe (inactivated virus), highly immunogenic, and efficacious. They induce seroconversion to protective level of antibody within 2 weeks after the initial dose

(40,41). Protective antibodies are present in 94% to 100% of adults 1 month after the first dose of hepatitis A vaccine (31). After the second dose, all persons had protective levels of antibody, which provide long-term protection (possibly 20 years or longer). The CDC notes that inactivated hepatitis A vaccines are 94% to 100% effective in preventing HAV infection (39). Hepatitis A vaccine is recommended for any person 2 or more years of age who is at increased risk of exposure to hepatitis A. Persons at risk include (a) travelers to countries where HAV is endemic; (b) military personnel; (c) certain ethnic or geographic populations with high rates of HAV (Native Americans, Alaskan people); (d) homosexual or bisexual men; (e) intravenous drug abusers; (f) regular recipients of blood or plasma-derived products (e.g., factor VIII); and (g) people engaged in high-risk employment (primate handlers, laboratory workers who handle HAV, employees of institutions for developmentally challenged, and staff of day care centers) (39). In addition, vaccination should be considered for persons with chronic liver disease (at greater risk for serious outcome of HAV infection) and food handlers (39). Pregnancy is not a contraindication to hepatitis A vaccine.

HEPATITIS B

HBV infection remains a major public health problem in the United States and worldwide (1,28,31,42). HBV infection is one of the most common causes of acute viral hepatitis, in the United States and worldwide (42). Acute HBV infection may be asymptomatic or may be associated with mild to severe clinically apparent acute hepatitis. Although most acute hepatitis B cases are self-limited and resolve, HBV infection may be persistent, often for the lifetime of the infected individuals (42). To a large extent, it is this characteristic of persistent chronic disease associated with serious long-term consequences that makes HBV such an important pathogen worldwide. In eastern Asian and sub-Saharan Africa, chronic HBV infection may exceed 10%, and HBV-associated liver disease is an important health problem where it is the most common cause of chronic liver disease and hepatocellular carcinoma (42).

HBV contains one of the smallest genomes among animal viruses, consisting of 3,200 base pairs (42). The nomenclature of hepatitis antigens and antibodies is summarized in Table 9.6. Hepatitis B infection is related to the presence of three morphologically distinct virus-like particles, as seen by electron microscopic studies (42,43 and 44). The 42-nm HBV is a DNA virus. The intact virus is termed the Dane particle. A 27-nm core contains the double-stranded DNA and is completely enveloped by the hepatitis B surface antigen (HBsAg). Excessive amounts of DNA-free HBsAg are synthesized by the liver cells of infected individuals and circulate freely in the serum as 20-nm spheres and tubules. This production of large amounts of viral antigen forms in the liver, which are detected in the blood during acute and chronic infection, is a unique characteristic of HBV infection (42). It is possible to isolate these various particles and produce antibodies to the antigens present. The HBsAg present on the tubular and spherical particles and on the surface of the Dane particle can be measured and is specific for hepatitis B; the corresponding antibody is that of hepatitis B surface antigen (i.e., anti-HBs). The core of the Dane particle contains the hepatitis B core antigen (HBcAg); its specific antibody is called anti-HBc.

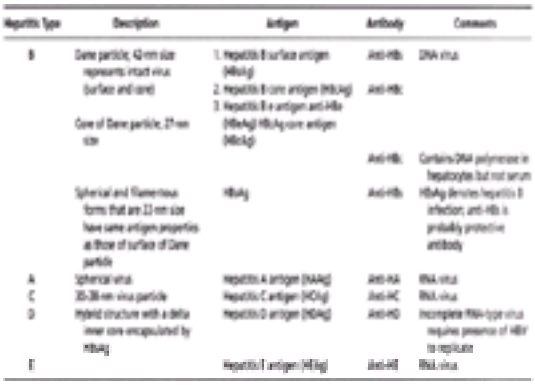


TABLE 9.6. NOMENCLATURE OF HEPATITIS ANTIGENS AND ANTIBODIES

An additional antigen-antibody system, the e system, has been described in HBV infection (42,45,46 and 47). The antigen is distinct from all known antigenic determinants of HBsAg and HBcAg but appears to be associated with the intact virus (Dane particle and high serum levels of hepatitis B viral-specific DNA polymerase activity). The e antigen appears early in almost all patients during the acute phase of HBV infection and may persist in patients in whom the infection progresses to chronic active hepatitis. Most importantly, several important prognostic and epidemiologic observations have been made with the e system. Persistent carriers of HBsAg who are positive for e antigen have a greater chance of developing chronic active hepatitis. Secondly, it has been demonstrated that HBsAg-positive blood that lacked e antigen but contained e antibody did not cause posttransfusion hepatitis, whereas e antigen–positive blood carried a significant risk for the development of posttransfusion hepatitis B. The third finding relates to pregnancy and vertical transmission of hepatitis B from mother to offspring. Mothers with e antigen–positive blood are much more likely (up to 90%) to transmit HBV to their children than those with HBsAg-positive, e antigen–negative blood (48). Thus, it seems likely that the presence of e antigen identifies the group that is highly infectious and at greater risk of transmitting HBV.

HBV infection occurs almost exclusively through contact with body fluids containing the virus (e.g., blood, semen, vaginal-cervical secretions). Individuals having contact with these fluids are at risk to acquire HBV. This includes intravenous drug abusers, health care workers, sexual partners of infected persons, patients undergoing hemodialysis, and infants born to mothers with HBV. The virus gains entry into susceptible persons via breaks in squamous epithelium or through mucous membranes. Although in developing countries, the most frequent route for HBV transmission is perinatal vertical transmission, in the United States, sexual contact is the most frequent mode. Detection of serum HBsAg has become the important diagnostic tool for identifying hepatitis B. HBsAg is present in approximately 1 per 1,000 adults in the United States and Europe (48). However, it is present in 2% to 25% of adults in tropical areas and Southeast Asia (28,42).

Hepatitis B is often a more severe infection than hepatitis A. HBV infection is transmitted predominantly by sexual contact, parenteral exposure, and vertical transmission from mother to newborn during the birth process (49). HBsAg has been

identified in urine, feces, seminal fluid, saliva, intestinal fluid, and gastric juice. Asymptomatic persistence of HBsAg, without abnormalities of liver function tests, is the most common form of HBV infection.

Before widespread use of HBV vaccines, the CDC estimated that approximately 300,000 primary HBV infections occurred annually in the United States (50,51 and 52). Approximately 40% to 45% of all cases of acute hepatitis in the United States were caused by HBV. Most acute HBV infections occurred in young adults, with one fourth associated with acute icteric disease (42). More than 10,000 HBV-infected persons were hospitalized annually and 300 died from fulminant hepatitis B (42). An estimated 6% to 10% (18,000 to 30,000 cases) of persons acutely infected with HBV became chronic carriers (51). In 1998, after more widespread use of HBV vaccine, a dramatic decrease in new HBV infections was reported (10,258 cases), with an estimated 185,000 new hepatitis B infections occurring (31). The incidence of acute hepatitis B infection varies in different populations in the United States (50,51). Persons at greatest risk include injection drug abusers, recipients of blood transfusions or certain other blood products (not all posttransfusion HBV infections are prevented by HBsAg screening), patients undergoing hemodialysis, laboratory personnel working with human blood or blood products, men having sex with men, those with multiple sexual partners, and medical and dental personnel with frequent contact with blood (Table 9.7). The lifetime risk for HBV infection was estimated to be 5% for the entire U.S. population before the widespread use of hepatitis B vaccines (42). During childbearing age, 70% of women in the United States are susceptible to hepatitis B. The frequencies of acute hepatitis B and chronic hepatitis B in pregnant women are 1 to 2 per 1,000 and 5 to 15 per 1,000, respectively (53). This risk for infection varies greatly, depending on occupation, socioeconomic status, history of drug abuse, or geographic factors.

1. Persons of Asian, Alaskan Eskimo, or sub-Saharan African descent
2. History of intravenous drug use
3. History of sexually transmitted diseases
4. Multiple sexual partners
5. Worker or patient in a hemodialysis unit
6. Health care or public safety worker
7. Household contact with hepatitis B carrier
8. Sexual contact with hepatitis B carrier
9. Worker or residence in an institution for the developmentally disabled
10. History of repeated blood transfusions
11. Residence in jail
12. Delivery to a carrier mother

TABLE 9.7. MAJOR RISK FACTORS FOR HEPATITIS B

Asymptomatic carriers of hepatitis B are estimated to number about 1 to 1.25 million in the United States, and 200 million worldwide are believed to serve as an epidemiologic reservoir for HBV infection (32,49). A large portion of these are in the populations of eastern Asia and sub-Saharan Africa, where the prevalence of chronic HBV infection is high and associated cirrhosis and liver cancer are major health problems (42). In the United States, approximately 4,000 to 5,000 persons die each

year from chronic HBV infection (3,000 to 4,000 with cirrhosis and 600 to 1,000 with liver cancer) (32,42). The medical and work-loss costs of HBV-related disease in the United States are estimated to be at least $700 million (32). The prevalence of serum anti-HBs indicates past HBV infection or vaccination. In the Unites States, this prevalence increases with age up to ages 30 to 45, to rates of 5% to 20% (42). Similar to the incidence of acute HBV infection, the prevalence of anti-HBs and other serologic markers of HBV infection differs in different population groups within the United States, and the groups at highest risk for acute HBV infection (Table 9.7) are those with the highest prevalence of anti-HBs (Table 9.8). Worldwide, the HBsAg carrier rate varies from 0.1% to 20% in different populations, with up to 20% of the population in highly endemic areas such as sub-Saharan Africa, eastern Asia, and Oceania being HBsAg carriers, and almost all HBsAg-negative adults have serologic evidence of past HBV infection (anti-HBs or anti-HBc) (42).

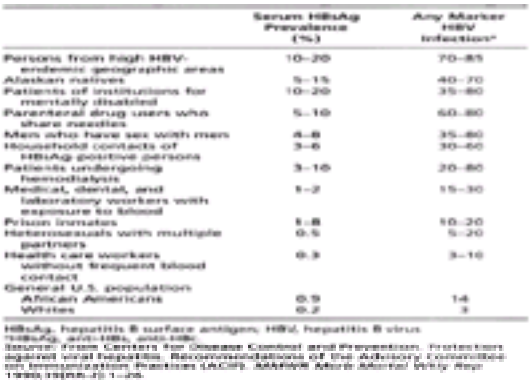


TABLE 9.8. PREVALENCE OF HEPATITIS B VIRUS SEROLOGIC MARKERS IN DIFFERENT U.S. POPULATIONS

Clinical Manifestations

Clinical manifestations of acute hepatitis B are similar to those described for hepatitis A (Table 9.4). The incubation period for hepatitis B ranges from 60 to 180 days. Fulminant hepatitis and death occur uncommonly (less than 1%) after acute hepatitis B. In 85% to 90% of patients, complete resolution of hepatitis B occurs with the development of protective levels of antibody (Fig. 9.2). The remaining 10% to 15% of individuals became chronically infected (chronic carriers) with HBV (Fig. 9.3). Among these chronic carriers (HBsAg positive), 15% to 30% develop chronic active or persistent hepatitis or cirrhosis (29). Thus, approximately 1.5% to 4.5% of hepatitis B cases will develop chronic liver disease. Hepatocellular carcinoma occurs in a small percentage of these chronic cases. The persons who remain seropositive for the hepatitis B e antigen (HBeAg) and/or who become superinfected with hepatitis D have a particular risk of developing chronic liver diseases (54,55). A chronic carrier state and chronic liver disease of more than 6 months' duration are recognized only for infection with hepatitis types B, C, and D. A large percentage of patients with primary hepatocellular carcinoma are positive for HBsAg (56). HBV is suspected to be oncogenic, and recently, the integration of viral DNA with cellular DNA of human

hepatocellular carcinoma has been demonstrated (11).

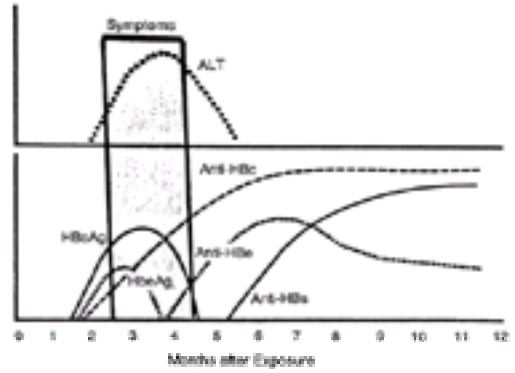


FIGURE 9.2. Serologic pattern with acute hepatitis B.

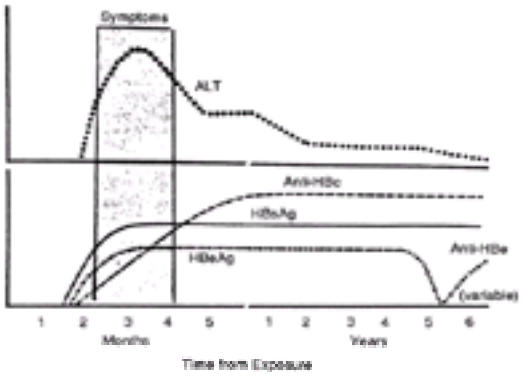


FIGURE 9.3. Serologic pattern with chronic hepatitis B.

Two major diseases are associated with chronic HBV infection. Persistent HBV infection may result in chronic persistent hepatitis or chronic active hepatitis. Factors that correlate with the severity of both acute and chronic hepatitis B include inoculum of virus and young age (42). Several mechanisms for hepatocyte injury have been proposed: (a) a human leukocyte antigen (HLA) class I–restricted cytotoxic T-cell response directed at HBcAg/HBeAg on HBV-infected hepatocytes; (b) a direct cytopathic effect of HBcAg expression in infected hepatocytes; (c) high-level expression and inefficient secretion of HBsAg; and (d) coinfection with HDV, another cytopathic virus (42).

Hepatocellular carcinoma is a second disease associated with chronic HBV infection. Although rare in most areas of the world, hepatocellular carcinoma is common in sub-Saharan Africa, Southeast Asia, Japan, Oceania, Greece, and Italy. The areas where hepatocellular carcinoma is common are those where HBV infection is common and persistent HBV infection at a high prevalence (42). Beasley et al. (11)

in a prospective study demonstrated that the incidence of hepatocellular carcinoma was more than 200 times higher in the HBsAg-positive group, compared with the HBsAg-negative group. Although the association of HBV infection with hepatocellular carcinoma is strong, a viral hepatocarcinogenic mechanism has not yet been elucidated (42).

Several other syndromes of extrahepatic disease are also associated with HBV infection. A serum sickness–like syndrome with fever, urticarial rash, arthralgias, and sometimes acute arthritis occurs in 10% to 20% of patients during the incubation period of acute hepatitis B. HBsAg–anti-HBs complexes appear to play a role in the pathogenesis of this entity (57,58). One third to one half of patients with polyarteritis nodosa have had persistent HBV infection (57,58). Similarly, many cases of membranous glomerulonephritis have been associated with chronic active hepatitis and persistent HBV infection (57,58). Some cases of essential mixed cryoglobulinemia have also been ascribed to HBV infection (59), but this association has been disputed (60).

Pregnancy and HBV Infection

Acute hepatitis B occurs in 1 to 2 of every 1,000 pregnancies, with an additional 0.5% to 1.5% of pregnant women being chronic carriers of HBV (i.e., HBsAg positive) (26). An estimated 20,000 infants are born to HBsAg-positive mothers annually in the United States, resulting in approximately 6,000 infants who become chronic carriers of HBV (61). Transmission of HBV from mother to infant during pregnancy (predominantly intrapartum) is one of the most efficient modes of HBV spread and often results in long-term sequelae such as cirrhosis and hepatocellular carcinoma (26,61,62). Maternal-infant transmission of HBV can occur via four routes. These include (a) transplacental (probably rare); (b) intrapartum; (c) postpartum; and (d) in breast milk or colostrum (63,64 and 65). Several investigations have demonstrated important epidemiologic and clinical aspects of HBV infection in the neonate (64,65 and 66). The predominant route for perinatal transmission of HBV is intrapartum via exposure to blood, genital secretions, and feces (Table 9.9). Approximately 80% to 90% of newborns of mothers with acute hepatitis B during the third trimester of pregnancy will become HBsAg positive (51,62,67). When maternal hepatitis occurs in early pregnancy, transmission of HBV to the neonate occurs in 10% of cases (51,62,67). Biochemical and histologic abnormalities often are present but are usually mild. Similarly, most newborns and infants infected with HBV are asymptomatic or present with mild clinical disease (62). Despite such benign-appearing clinical and laboratory findings, persistence of HBsAg occurs and has been associated with chronic hepatitis and cirrhosis.

Clinical Status	Transmission Rate
HBsAg+, HBeAg–	10–20%
HBsAg+, HBeAg+	90%
Acute hepatitis B first trimester	10%
Acute hepatitis B third trimester	80–90%

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen.

TABLE 9.9. PERINATAL TRANSMISSION RATES OF HEPATITIS B VIRUS

Several studies have documented that the crucial determinant of vertical transmission from mother to newborn is the presence of an e antigen (Table 9.9) (44,48,49,68,69 and 70). HBeAg-positive mothers have high levels of virus and are more likely to transmit it to their offspring. Lee et al. (69) reported that 26 of the 37 infants (70.3%) born to HBeAg-positive mothers were HBsAg positive by 5 months of age. Beasley et al. (70) noted that all the infants who were chronic HBsAg carriers were born to HBeAg-positive mothers. In addition, nearly all babies born to HBeAg-positive mothers became infected with HBV during the first year of life, and 85% become chronic HBsAg carriers. Data from the United States concur with data from Asia and support the finding that HBeAg is predictive of vertical transmission (71). In the United States, the likelihood of acquiring perinatal HBV infection is 70% to 90% for infants born to mothers who are positive for HBsAg and HBeAg. Further, 85% to 90% of infected infants will become chronic carriers. However, infants of mothers who are HBsAg positive but HBeAg negative may also become infected (estimated risk, 5% to 10%) and develop severe, even fatal, hepatitis B (72). In contradistinction to adults, in whom 10% become chronic carriers of HBV, in neonates infected with HBV, 85% become chronic carriers and are thus exposed to the risk of chronic liver disease and hepatocellular carcinoma. Combined with the 30% to 40% transmission rate by maternal chronic carriers in endemic areas such as Asia, the public health implications of perinatally acquired hepatitis B are massive and evident. In the United States and other Western industrialized countries, hepatitis is documented in approximately 10% of neonates born to mothers who are chronic carriers of HBsAg. In areas of the world (Taiwan and Japan) where maternal asymptomatic carriers are more common, higher rates of neonatal transmission occur (66,73). Thus, in Asia, 30% to 40% of chronic carriers transmit HBV to their newborn infants (74). Schweitzer et al. (65) in the United States reported that only 1 of 21 infants born to HBsAg-positive mothers become HBsAg positive themselves. Studies from Denmark (75) and Greece (76) have confirmed this low risk of transmission for Western societies. However, in Taiwan, Stevens et al. (66) demonstrated that 40% of infants born to HBsAg carrier mothers were HBsAg positive. Okada et al. (73) provided similar high rates of transmission in their study of Japanese HBsAg carriers. In summary, the factors that are associated with an increased risk of vertical transmission of HBV include (a) high maternal viral load, including high titer levels of HBsAg; (b) presence of e antigen; and (c) high HBV DNA levels (26). The highest risk (70% to 100%) is in infants born to mothers who are HBsAg and e antigen positive. On the other hand, the lowest risk (less than 10%) is

associated with presence in the mother of antibody to e antigen (26).

There is no evidence that HBV infection is any more common in pregnancy. In a well-nourished healthy population, the mortality rate from hepatitis B is low and no greater in pregnant than in nonpregnant individuals (49). Where malnutrition is a problem, the mortality rate is much higher but still is similar in pregnant and nonpregnant women. The incidence of spontaneous abortion during the first trimester in patients with acute viral hepatitis has reportedly increased. Similarly, when viral hepatitis occurs during the third trimester, there is a reported increased incidence of preterm labor (64). However, the incidence of spontaneous abortion and preterm delivery is probably no higher with hepatitis than with other febrile illnesses. Pastorek et al. (77) confirmed that HBs-antigenemia (i.e., chronic HBsAg) had no adverse effect on perinatal outcome. Although transplacental passage of hepatitis virus has been established, teratogenic damage has never been demonstrated for hepatitis B (62).

Diagnosis

The diagnosis of HBV infection relies on serologic markers (Fig. 9.2 and Table 9.2). Evaluation of patients for acute and past HBV infection includes tests for serum HBsAg anti-HBs, anti-HBc, and IgM anti-HBc. The diagnosis of acute hepatitis B is confirmed by detecting HBsAg and IgM anti-HBc. HBsAg first appears in the serum during the incubation period, persists throughout the clinical illness, and disappears with resolution of disease. However, in a small number of patients, HBsAg is cleared rapidly and is absent when the patient presents clinically. Although anti-HBs and anti-HBc can be detected, both are long lived and therefore may represent preexisting rather than current acute HBV infection. Chau et al. (78) have developed an immunoassay for IgM anti-HBc that is helpful for the diagnosis of acute HBV infection in patients who rapidly clear HBsAg. In addition, patients with acute HBV infection develop HBeAg, HBV DNA, and DNA polymerase. These are all markers of active viral replication. In Table 9.10, commonly encountered serologic patterns associated with HBV infection are enumerated.

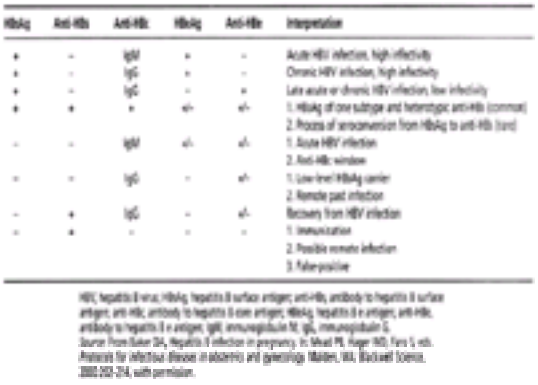


TABLE 9.10. COMMONLY ENCOUNTERED SEROLOGIC PATTERNS OF HBV INFECTION

Approximately 5% to 10% of patients with HBV infection do not clear HBsAg and become chronic HBsAg carriers (Fig. 9.3) (1). As many as 0.2% to 1.0% of adults in the United States are chronic HBsAg carriers. Among high-risk groups such as male homosexuals, hemophiliacs, intravenous drug abusers, and patients undergoing renal dialysis, the prevalence of HBsAg is even higher. As noted by Dinsmoor (26), the most common occurrence is that an asymptomatic pregnant woman is found to be HBsAg positive at her initial prenatal screening. In this instance, the clinician must determine whether this reflects a chronic carrier state or an acute infection. Generally, when symptoms of acute hepatitis or a history of recent exposure to HBV is absent, such cases usually represent a chronic carrier state (26). An algorithm for assessing persons found to be HBsAg positive is presented in Fig. 9.4.

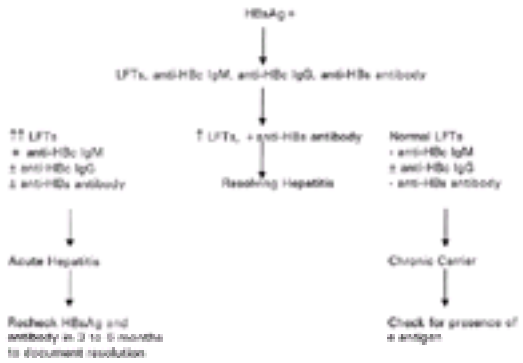


FIGURE 9.4. Algorithm for evaluation of HBsAg-positive patients. HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; LFTs, liver function tests. (From Dinsmoor MJ. Hepatitis in the obstetric patient. *Infect Dis Clin North Am* 1997;11:77–91, with permission.)

In neonates, clinical illness with perinatally acquired hepatitis B is relatively infrequent, and most commonly, HBV infection in the neonate is asymptomatic chronic hepatitis with the presence of HBsAg in serum, abnormal liver enzyme levels, and histologic evidence of unresolved hepatitis (18). Among these asymptomatic infants, approximately 10% may become icteric at 3 to 4 months of age.

Treatment

Similar to other forms of acute viral hepatitis, there is no specific therapy for acute hepatitis B. Management is primarily supportive care on an ambulatory basis with bed rest, a high-protein diet, and avoidance of hepatotoxic drugs. The acute illness with HBV is usually self-limiting, although 5% to 10% of individuals go on to become chronic carriers of HBV. In the rare instance in which fulminant hepatitis, encephalopathy, or coagulopathy occurs, hospitalization, preferably in an intensive care unit, is necessary.

With chronic hepatitis B, the goals of therapy are suppression or complete resolution of chronic active hepatitis, halting progression of liver disease and converting patients to a noninfectious state (42). To that end, partial success has been achieved with the development of antiviral therapy for HBV and has resulted in Food and Drug Administration–approved licensing in the United States of two antiviral agents for treatment of chronic hepatitis B: recombinant interferon alpha (IFN-a) and the nucleoside analog lamivudine. Three types of responses have been described with antiviral therapy of chronic hepatitis B (79,80,81). With type I response (small fraction of cases), all markers of infection in serum (HBsAg, HBeAg, virion DNA polymerase, virion DNA, and infectious HBV) and liver (HBcAg and HBsAg) become undetectable during treatment and remain so indefinitely after therapy is discontinued. In type II response, HBeAg, virion DNA polymerase, virion DNA, and infectious HBV disappear from serum; HBcAg disappears from the liver; and anti-HBe appears during treatment. These responses are permanent after treatment ceases, but HBsAg persists in serum and liver. Most patients have the type III response, in which virion DNA polymerase, virion DNA levels, and HBeAg are partially suppressed during treatment but return to pretreatment levels when treatment is stopped. Type I and type II are clinically significant responses with improvements in liver function and histologic findings and elimination of infectious HBV from the serum of all (or most) patients (40,82,83). Unfortunately, currently available antiviral therapies do not (in most cases) eliminate detectable serum HBsAg, which is a marker for an increased risk of liver cancer developing in these patients (42). The availability of lamivudine as an oral agent with acceptable side effects provides a major alternative to parenteral IFN-a and its associated side effects (84,85 and 86). Oral lamivudine dosages of 100 mg one to three times per day for up to 4 to 6 months are recommended (42). More recently, famciclovir (approved for therapy of herpes) has also been shown to strongly suppress HBV replication (87).

Prevention

Although there are no specific antiviral therapies currently available for treatment of acute hepatitis B, there are excellent preventive measures, including passive immunization with hepatitis B immune globulin (HBIG) and active immunization with vaccine. Full use and application of these prevention methods would have a significant favorable public health impact. The risk of acquiring hepatitis B is greatest for those exposed to patients with hepatitis or blood containing HBsAg, and particularly HBeAg; examples include household contact, sexual contact, hospital exposures, and inoculation with contaminated needles. In addition, infected pregnant women may transmit the virus to their fetus. Those groups who have an increased risk of HBV infection and for whom hepatitis B vaccine is recommended are listed in Table 9.11 (51,88). However, the policy of vaccination of high-risk groups had little impact on the incidence of new HBV infections (42). This finding, plus the overwhelming evidence of safety of the available recombinant DNA hepatitis B vaccines, led the CDC to recommended universal vaccination of all newborn infants in the United States in 1991 (88). Because HBV infection continued to occur among adolescents and young adults (11 to 21 years old), in 1996 the Advisory Committee on Immunization Practices, the American Academy of Pediatricians, the American Academy of Family Practice, and the American Medical Association jointly recommended hepatitis B vaccination of adolescents 11 to 12 years old not previously vaccinated. In addition, women with definite exposure to HBV should be tested for preexisting antibody to HBV. If they are seronegative, they should be given

HBIG. This is given in a single dose of 0.06 mL per kilogram of body weight as soon as possible after exposure, followed by vaccination with recombinant hepatitis B vaccine. Simultaneous administration of HBIG does not impair the response to vaccine.

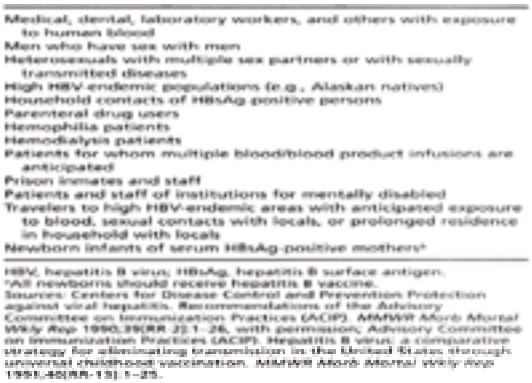
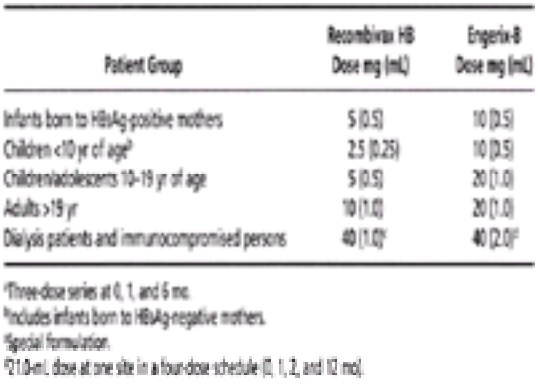

Medical, dental, laboratory workers, and others with exposure to human blood
Men who have sex with men
Heterosexuals with multiple sex partners or with sexually transmitted diseases
High HBV endemic populations (e.g., Alaskan natives)
Household contacts of HBsAg positive persons
Parenteral drug users
Hemophilia patients
Hemodialysis patients
Patients for whom multiple blood/blood product infusions are anticipated
Prison inmates and staff
Patients and staff of institutions for mentally disabled
Travelers to high HBV-endemic areas with anticipated exposure to blood, sexual contacts with locals, or prolonged residence in household with locals
Newborn infants of serum HBsAg-positive mothers[a]
HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.
[a]All newborns should receive hepatitis B vaccine.
Source: Centers for Disease Control and Prevention Protection against viral hepatitis. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1990;39(RR-2):1–26, with permission; Advisory Committee on Immunization Practices (ACIP). Hepatitis B virus: a comparative strategy for eliminating transmission in the United States through universal childhood vaccination. MMWR Morb Mortal Wkly Rep 1991;40(RR-13):1–25.

TABLE 9.11. GROUPS AT INCREASED RISK OF HEPATITIS B VIRUS INFECTION AND FOR WHOM HEPATITIS B VACCINE IS RECOMMENDED

Currently, there are two clinically available recombinant formulations of the hepatitis B vaccine: Recombivax HB (Merck, West Point, PA) and Engerix-B (SmithKline Beacham, Philadelphia, PA). The original Heptavax (Merck, West Point, PA) is no longer available in the United States but is in China and some other countries. The recommended dosing of these vaccines is presented in Table 9.12 (51). Anti-HBs responses with these dosage schedules are excellent, with more than 90% of persons younger than 40 to 50 years having high antibody titers after the third vaccine dose (42). Lower responses are seen with older age, obesity, heavy smoking, and immunologic impairment. Although anti-HBs titer levels fall over time after vaccination, HBV infections that may occur when titer levels are less than 10 mIU/mL (undetectable) are always subclinical and usually without detectable serum HBsAg (89,90). Thus, even when the titer level of anti-HBs has fallen to undetectable levels, protection against disease remains even if HBV infection occurs (42). The question of whether regular booster doses are required, and if so at what interval, remains unanswered (42).


Patient Group	Recombivax HB Dose mg (mL)	Engerix-B Dose mg (mL)
Infants born to HBsAg positive mothers	5 (0.5)	10 (0.5)
Children <10 yr of age[b]	2.5 (0.25)	10 (0.5)
Children/adolescents 10–19 yr of age	5 (0.5)	20 (1.0)
Adults >19 yr	10 (1.0)	20 (1.0)
Dialysis patients and immunocompromised persons	40 (1.0)[c]	40 (2.0)[d]

[a]Three-dose series at 0, 1, and 6 mo.
[b]Includes infants born to HBsAg-negative mothers.
[c]Special formulation.
[d]2.0-mL dose at one site in a four-dose schedule (0, 1, 2, and 12 mo).

TABLE 9.12. RECOMMENDED DOSING OF HEPATITIS B VIRUS VACCINES[a]

The availability of effective and safe vaccines provides health care workers the opportunity to prevent neonatal HBV infection and the serious consequences associated with chronic hepatitis B (61). The combined use of passive (HBIG) and active immunization (vaccine) has been demonstrated to be 85% to 95% effective in preventing neonatal HBV infection (51,71,91). Initially, the CDC only recommended screening pregnant women for asymptomatic HBV infection (HBsAg positive) selectively based on the risk criteria listed in Table 9.7. However, multiple studies in the late 1980s demonstrated that selective screening failed to identify one half to two thirds of HBsAg-positive mothers (92,93 and 94). As a result, in 1988 the CDC recommended universal screening of all pregnant women (72). Because the risk of vertical transmission is reasonably high (10% to 20%) in HBsAg but HBeAg-negative mothers, only HBsAg is screened for (72). Most recently, the CDC has recommended universal vaccination of all infants against HBV (88). However, the dosage recommendations depend on the mother's serum status (Table 9.12). Thus, the CDC and the American College of Obstetricians and Gynecologists recommend that all pregnant women still need to be screened for HBsAg during pregnancy (72,88,95). Infants born to seropositive mothers should receive HBIG (0.5 mL intramuscularly) and hepatitis vaccine within 12 hours of birth, with additional vaccine doses at 1 to 2 and 6 months of age (88). The doses of Recombivax HB and Engerix-B are 5 mg (0.5 mL) and 10 mg (0.5 mL), respectively (88). In the case of seronegative mothers, HBIG is not necessary, but the first vaccine dose should be administered before the newborn leaves the hospital and subsequent doses are given at 1 to 2 and 6 months (which can be modified slightly to coincide with timing of other infant immunizations). The recommended doses with seronegative mothers of Recombivax HB and Engerix-B are 2.5 mg (0.2 mL) and 10 mg (0.5 mL), respectively (88).

In cases in which the mother's serum status is unknown, at the time of delivery, a serum sample should be obtained. Until the results are available, the mother is assumed to be HBsAg positive and her infant should receive HBIG and hepatitis B vaccine within 12 hours of birth. The subsequent doses are then adjusted according to the mother's serum status.

Such treatment is effective in preventing 85% to 95% of the HBV chronic carrier state (61). Arevalo and Washington (96) demonstrated the cost effectiveness of prenatal screening and immunization for HBV. More recently, Margolis et al. (97) performed an economic analysis of the current recommendations for prevention of HBV transmission by immunization. They noted that prevention of perinatal infection and routine infant vaccination would lower the 4.8% lifetime risk of HBV infection by at least 68%, compared with a 45% reduction with adolescent vaccination. These authors demonstrated that vaccination to prevent perinatal HBV infection was most cost effective, requiring a cost per year of life saved of $164, compared with $1,522 for infant vaccination and $3,730 for adolescent vaccination (97). The public health impact of mass (universal) vaccination to prevent perinatal HBV infection was clearly demonstrated by Chen et al. (98), who reported that after the mass vaccination program in Taiwan, the overall prevalence rate of HBsAg decreased from 9.8% in

1984 to 1.3% in 1994 and the overall prevalence of anti-HBc from 26% in 1984 to 4.0% in 1994 (98).

HBV infection secondary to exposure to infected patients is a major concern for health care workers. In the past, it was estimated that approximately 12,000 health care workers annually in the United States contract hepatitis B as a result of a needle stick or splash of body fluid (e.g., amniotic fluid or blood) to a mucous membrane (51,99). Each year, approximately 200 of these health care workers developed fulminant hepatitis and died (51,99). An additional 1,200 health care workers became chronic carriers of hepatitis B as a result of occupational exposure. Clearly hepatitis B is a much more infectious agent and a much greater threat to health care workers than human immunodeficiency virus (HIV) infection.

There are several reasonably easy ways for health care workers to protect themselves. The most important method is for all health care workers to be vaccinated for hepatitis B. If exposed via an occupational injury, their level of immunity should be determined, and if it is waning or absent, HBIG and a booster dose of vaccine should be administered. For workers who have not been vaccinated or do not have natural acquired immunity, they should receive postexposure HBIG (0.06 mL/kg intramuscularly) as soon as possible (less than 24 hours) and commence a vaccine series (Table 9.12). Secondly, health care workers should consistently and compulsively adhere to universal precautions for body fluids to prevent sharp injuries (needles, scalpels) and splashes of body fluids to exposed mucous membranes or skin (100). Thirdly, health care workers should encourage patients (with our without known risk factors) to receive vaccination for hepatitis B (29).

It is equally important to recognize that health care workers who are infected with hepatitis B are a risk to their patients and must observe safeguards to prevent transmission of HBV infection (101). The risk of transmission is greatest for invasive surgical procedures during which the surgeon (or assistant) sustains a sharp injury resulting in bleeding. Gynecologic surgical procedures deep in the pelvis are particularly at risk. As noted by Simms and Duff (102), unless the patient has documented immunity to hepatitis B (vaccination or previous infection), there exists an ethical obligation on behalf of the health care worker to inform the patient that some risk of transmission exists. The surgeon or assistants must take precautions to minimize the risk of an injury by a sharp object (e.g., double glove, only instruments handle needles). However, if any injury does occur, the patient should immediately be offered HBIG and hepatitis B vaccine.

HEPATITIS C

The ability to identify the antigens and their antibody responses in both hepatitis A and hepatitis B led to the concept that not all clinical cases of acute hepatitis infection were due to these agents. As a result, the concept of non-A, non-B viral hepatitis was developed (103,104). Two major epidemiologic patterns of disease were described for non-A, non-B hepatitis. The first posttransfusion (parenterally transmitted) non-A, non-B hepatitis case was demonstrated to occur in epidemiologic situations very similar to those of HBV (105). More recently, an enterically transmitted form of non-A, non-B hepatitis (i.e., HEV) has also been recognized (106). The cloning of portions of the genome of a non-A, non-B hepatitis agent provided justification for naming this agent hepatitis C (107). Expression of a

recombinant HCV-derived sequence formed the basis for a serologic assay of this agent (108).

Epidemiology

HCV is now recognized as the major etiologic agent of the parenterally transmitted form of non-A, non-B hepatitis (105,107,108,109,110,111,112,113,114,115,116,117 and 118). It is estimated that hepatitis C is responsible for 20% to 40% of cases of acute viral hepatitis (112,113,119). HCV is the most common chronic bloodborne infection in the United States (113). During the 1980s, the CDC estimated that an average of 230,000 new HCV infections occurred annually (113). Since the peak in 1989 after introduction of HCV screening by blood banks, the annual numbers of acute HCV infection have decreased by more than 80%, to an estimated 36,000 cases in 1996 (113,120). Currently, approximately 30,000 acute new infections are estimated to occur each year (112). However, only 25% to 30% of these acute infections with HCV are diagnosed (112).

In developed countries, HCV prevalence is typically 1% to 2% in the general population and less than 0.5% among blood donors (115). The third National Health and Nutrition Examination Survey (NHANES III) provided an accurate estimate of hepatitis C prevalence in the United States (121). The overall prevalence of antibody to HCV (anti-HCV) was 1.8%, corresponding to an estimated 3.9 million persons nationwide (95% confidence interval [CI], 3.1 million–4.8 million) with HCV infection (121). Seventy-four percent of anti-HCV–positive persons were positive for HCV RNA, indicating that 2.7 million persons in the United States (95% CI, 2.4 million–3.0 million) had chronic HCV infection (121). The prevalence of HCV infection in the United States is higher among racial minorities than in White Americans and greater in African Americans than in Hispanics (121). However, these differences are primarily due to socioeconomic factors, with lower socioeconomic status being strongly associated with HCV infection. Thus, racial ethnic group was not independently associated with HCV infection (121). Similarly gender was not associated with HCV infection (121). In NHANES III, most HCV infections could be attributed to the use of illegal drugs or high-risk sexual behavior (121).Worldwide, it is estimated that more than 170 million persons are infected with HCV (122).

Population-based studies have demonstrated that 40% of chronic liver disease is HCV related (116). Chronic HCV infection develops in 75% to 85% of patients after acute HCV infection (113,123). Chronic hepatitis C is responsible for an estimated 8,000 to 10,000 deaths annually in the United States (113). Because most HIV-infected persons are in the 30- to 49-year-old age-group, the CDC projects that the number of deaths attributable to HCV-related chronic liver disease may increase substantially in the next 10 to 20 years as this group of HCV-infected persons reaches ages at which complications from chronic liver disease typically occur (113). These complications include cirrhosis, which occurs in 10% to 20% of persons with chronic HCV infection over a 20- to 30-year period, and hepatocellular carcinoma, which occurs in 1% to 5% (112,113). However, once cirrhosis is established, the rate of development of hepatocellular carcinoma might be as high as 1% to 4% per year (112,113). The CDC estimates that the medical and work-loss costs of HCV-related acute and chronic liver disease are more than $600 million annually and that HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults (113). The disease burden associated with HCV infection in the United States is summarized in Table 9.13. In developing countries

where the prevalence of HCV infection is much higher (ranging from 4% to 6% in low-risk groups), the disease burden of HCV infection is significantly increased (114,124).

Estimated number of acute HCV infections, 1997	30,000–38,000 (112,113,116,121)
Estimated number of acute clinical cases, 1997	6,300 (116,121)
Fulminant cases of acute HCV infection	Rare
Prevalence anti-HCV	1.8% (121)
Number of persons ever infected	3.9 million (121)
Number of persons with chronic infection*	2.7 million (121)
Estimated number of chronic HCV related deaths annually	8,300–10,000 (113)
Percentage of chronic liver disease related to HCV infection	40% (113)

*Persistent elevated alanine aminotransferase levels and/or presence of HCV RNA in serum.
Source: From Williams I. Epidemiology of hepatitis C in the United States. Am J Med 1999;107(6B):2S–9S, with permission.

TABLE 9.13. DISEASE BURDEN ASSOCIATED WITH HEPATITIS C VIRUS (HCV) INFECTION IN THE UNITED STATES

HCV is transmitted parenterally, usually by transfusion, intravenous drug abuse, and accidental needle sticks (124). However, as demonstrated by Alter et al. (125), a recognized parenteral exposure accounts for only 50% of the reported cases of hepatitis C. Both sexual transmission (126,127,128,129,130,131,132,133,134,135 and 136) and vertical transmission (137,138,139,140,141,142 and 143) have been suggested as alternative modes for transmission of HCV.

Risk factors associated with transmission of HCV in the United States were identified in case-control studies during the early 1980s and included blood transfusion, intravenous drug abuse, employment in patient care or clinical laboratory work, exposure to a sex partner or household member with a history of hepatitis, exposure to multiple sex partners, and a low socioeconomic level (113,114). The CDC has estimated the prevalence of HCV infection in the United States according to various demographic characteristics (Table 9.14) (113). The relative importance of risk factors for transmission of HCV has changed dramatically since the early 1980s when blood transfusions were responsible for approximately 40% of new cases of hepatitis C (116). Currently, HCV is rarely transmitted by blood transfusion in the United States (113). Since the implementation of routine testing of donors for HCV infection in 1990 and the introduction of more sensitive multiantigen testing in 1992, the risk of HCV infection is estimated to be 1 per 100,000 U of transfused blood (144,145), and blood transfusion now causes less than 4% of HCV infections in the United States (120,145). In the United States, injection drug abuse currently is the most common risk factor for transmission of HCV (113) and accounts for approximately 60% of HCV transmission (116). Alter (120) reported that since 1992, illicit drug abuse has been associated with at least two thirds of new HCV infections in the United States. Data are conflicting and it is unknown whether persons with a history of noninjection illegal drug abuse (e.g., intranasal cocaine abuse) are at increased risk for HCV (113,116). Approximately 20% of persons with HCV infection report sexual exposures in the absence of percutaneous risk factors (116). Other

known factors (occupational, hemodialysis, household, perinatal) together account for approximately 10% of HCV infections (116).

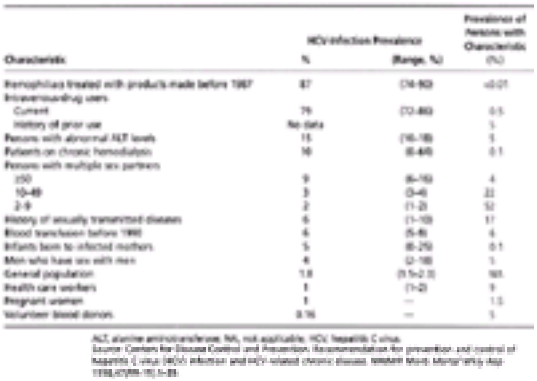


TABLE 9.14. ESTIMATED AVERAGE PREVALENCE OF HCV INFECTION IN THE UNITED STATES BY VARIOUS CHARACTERISTICS AND ESTIMATED PREVALENCE OF PERSONS WITH THESE CHARACTERISTICS IN THE POPULATION

Etiology

HCV is a single-stranded RNA virus approximately 50 nm in diameter (105). Although its structure, genomic organization, and replication cycle are similar to the those of the Flaviviridae family viruses, HCV is distinct enough to be classified within a separate novel genus *Hepacivirus* (105,114). HCV is characterized by striking genetic heterogeneity that includes six major genotypes, with numerous subtypes (more than 80) and minor variants called “quasi-species” (minor molecular variations with only 1% or 2% nucleotide heterogeneity) (146,147). As a result of the high level or virion turnover and the absence of proofreading by the RNA polymerase, NS5B, rapid accumulation of mutations within the viral genome occur (105,147). Thus, multiple variants of HCV can be recovered from the plasma and liver of an infected person at any time (105). The most commonly used classification system is that of Simmonds et al. (148), consisting of 6 major genotypes and 11 subtypes (1a–c, 2a–-c, 3a, 3b, 4a, 5a, and 6a) (148). The most common HCV subtypes found in the United States are 1a and 1b, which represent 58% and 22%, respectively, of all HCV infections (149).

Little is known about the details of HCV replication because there is no permissive cell culture system in which the replication cycle can be directly studied (105). It is presumed that the hepatocyte is the primary site for replication of HCV and is a major source of virus in the blood (105). Although debated, HCV may also replicate within peripheral mononuclear cells of lymphoid or bone marrow origin (105).

Clinical Manifestations

The incubation time for acute HCV infection is usually 30 to 60 days (range, 15 to

150 days). HCV RNA can be detected in blood within 2 weeks of exposure. Most HCV infections are asymptomatic (75%) and only 25% present with symptoms. Clinical presentation of acute HCV infection is similar to that seen with other forms of acute viral hepatitis. Symptomatic patients present with malaise, fever, abdominal pains, and jaundice. However, these symptoms are generally milder than those seen in patients with HBV infection. Extrahepatic manifestations are uncommon in acute HCV infection (105). In the United States and other Western countries, fulminant hepatitis due to HCV is very uncommon (105). Resolution of clinical symptoms and abnormal serum liver chemistries occur 3 to 4 months after the onset of jaundice. Approximately 85% of patients infected with HCV do not resolve their infection and progress to chronic hepatitis (i.e., persistence of HCV RNA in blood with or without elevated alanine transaminase levels).

Chronic hepatitis C may be accompanied by fatigue, weakness, or hepatic failure (102,105,114,150). Most patients with persistent chronic hepatitis C are asymptomatic for life. However, many quality-of-life indexes are reduced in HCV-infected persons, even in the absence of cirrhosis, and they improve with successful therapy (151).

Persistent or fluctuating ALT elevations indicating active liver disease develop in 60% to 70% of patients with chronic HCV infection (113). ALT levels are within the normal reference range in the remaining 30% to 40% of chronically infected persons. The course of chronic HCV infection is usually insidious and progresses slowly without symptomatic or physical signs in most cases during the first two or more decades after acute infection (113). By 20 to 30 years, cirrhosis develops in 10% to 20% of persons chronically infected with HCV, and hepatocellular carcinoma develops in 1% to 5% (113). Among patients with established cirrhosis, hepatocellular carcinoma may develop in 1% to 4% per year (113). Approximately 10% to 20% of HCV-infected persons with cirrhosis decompensate clinically within 5 years (105,152,153). It is not possible to predict which HCV-infected persons will develop cirrhosis and which patients with cirrhosis will develop decompensated liver disease or hepatocellular carcinoma (105). Recent data suggest that increased alcohol intake, age older than 40 years at infection, and male sex are associated with more severe liver disease (154). Histologic examination of the liver remains the best indicator of the stage of disease (105).

Pregnancy and HCV

The seroprevalence of HCV among pregnant populations in the United States has ranged from 2.3% to 4.6% (138,139,155). Among cohorts of HIV-infected pregnant women, the seroprevalence of HCV has been reported to range from 17.1% to 54% (156,157 and 158). This is higher than the 1.8% reported for the general population (121) or the 0.16% in volunteer blood donors (113). Among the pregnant population, risk factors for HCV include history of intravenous drug abuse, history of multiple sexually transmitted diseases (STDs), HBV infection, maternal age older than 22.5 years, sexual partner who abuses intravenous drugs, and three or more lifetime sex partners (158). No risk factors were present in 13% of the patients (139). Silverman et al. (159) estimated that using factors to screen for HCV would fail to detect half of all anti-HCV–positive prenatal patients. Leiken et al. (155), using nine epidemiologic predictors (intravenous drug abuse, other drug abuse, age of older than 30 years, incarceration, blood transfusion, STD, previous hepatitis, HIV seropositivity, and intravenous drug-abusing sex partner), reported that 74 of 75 prenatal patients

seropositive for HCV were identified (sensitivity, 98.7%), thus, reducing the cost of screening by 55%.

Pregnancy usually does not affect the clinical course of acute or chronic hepatitis C. Similarly, neither acute hepatitis C nor chronic persistent hepatitis C has been associated with an adverse effect on the mother or fetus (102,139,160,161). On the other hand, chronic active hepatitis is associated with an increased incidence of preterm delivery and intrauterine growth retardation (102,164). With cirrhosis, the maternal mortality rate is increased (160). In addition, with fulminant hepatitis, significant maternal and fetal morbidity and mortality occur (160). Recently, Hershow et al. (157) reported that the perinatal transmission of HIV might be higher in women coinfected with HCV.

The role of vertical transmission of HCV is controversial and reported investigations have been conflicting. Unlike that of HBV infection, vertical transmission of HCV, as suggested by most studies, is infrequent (113,114). Thaler et al. (141) and Navati et al. (142) demonstrated that in the presence of coinfection in mothers with HIV and HCV, perinatal transmission of HCV occurs at a high frequency. Lin et al. (143) proposed that this finding suggests that mother-to-infant transmission might be related to the increased HCV viremia in HIV-infected or otherwise immunosuppressed mothers. Moreover, they suggested that a high level of maternal HCV viremia might play an important role in determining the efficacy of vertical transmission (143).

The information available regarding vertical transmission of HCV has increased dramatically over the past decade (114). Vertical transmission rates have varied widely. In part, this is due to earlier studies that were retrospective and used anti-HCV. More recent investigations have been prospective and used HCV RNA as a marker of neonatal infection. Watts (117) recently reviewed studies assessing the risk of vertical transmission of HCV. She noted that the risk of transmission from HCV-seropositive pregnant women to their infants was 6.9% (32 of 461 infants), with a range of 0% to 20%. In more recent studies, the rate of transmission among women with HCV RNA detectable during pregnancy was 45 (19%) of 240 women, compared with 1 (0.9%) of 115 women without detectable HCV RNA (117). As noted earlier, coinfection with HIV increased the risk of perinatal transmission of HCV and transmission seemed to correlate with the level of maternal viremia, with the highest risk seen in women with HCV viral loads exceeding 5 million copies per milliliter. Vertical transmission of HCV has not been demonstrated in pregnant women who are anti-HCV positive but HCV RNA negative (162,163 and 164). In Table 9.15, the risk of vertical transmission of HCV in HIV-negative, HCV RNA–positive pregnant women is shown. The overall risk averaged 4.8%, ranging from 0% to 33% among HIV-negative women. The CDC reported similar results, demonstrating that the average rate of HCV infection among infants born to HCV-positive, HIV-negative women is 5% to 6% (range, 0% to 25%) (113). Significantly higher rates of vertical transmission have been reported in women coinfected with HCV and HIV than in those only infected with HCV (142,163,164,165,166,167,168,169,170,171,172,173,174 and 175). The CDC noted that the vertical transmission rate in coinfected women was 14% (range, 5% to 36%) and 17% based on detection of anti-HCV and HCV RNA, respectively (113). In Table 9.16, the risk of vertical transmission of HCV in seropositive HCV RNA–positive pregnant women is shown. The overall risk among HIV-positive women was 20.4%,

ranging from 8.9% to 67%.

Study	Mothers HCV Antibody-Positive	Mothers HCV-RNA–Positive (%)	Newborn HCV-RNA-Positive (%)
Wejstal et al., 1992 (137)	21	21	1 (4.8)
Marcellin et al., 1993 (164)	26	10	0
Lin et al., 1994 (140)	15	15	1 (6.6)
Ohto et al., 1994 (145)	53	51	5 (9.7)
Manzini et al., 1995 (166)	27	15	0
Paccagnini et al., 1995 (167)	17	6	2 (33.3)
Morlya et al., 1995 (168)	103	84	2 (2.3)
Zanetti et al., 1995 (165)	54	46	0
Zuccotti et al., 1995 (163)	17	8	2 (25)
Matsubara et al., 1995 (170)	29	19	3 (15.7)
Maccabruni et al., 1995 (162)	14	12	3 (25)
Pigan et al., 1996 (171)	25	18	0
Fiehler et al., 1996 (172)	53	35	0
Zanetti et al., 1995 (164)	251	176	8 (4.5)
La Torre et al., 1998 (173)	80	56	2 (3.6)
Totals	805	560 (69.2)	27 (4.8)

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

TABLE 9.15. RISK OF VERTICAL TRANSMISSION OF HCV IN HIV-NEGATIVE HCV-RNA–POSITIVE PREGNANT WOMEN

Study	Mothers HCV Antibody-	Mothers HCV-RNA-Positive	Newborns HCV-RNA-Positive (%)
Novati et al., 1992 (142)	8	6	4 (67)
Manzini et al., 1995 (166)	18	8	1 (12.5)
Paccagnini et al., 1995 (167)	53	17	12 (70.3)
Zanetti et al., 1995 (169)	22	18	8 (44.4)
Zuccotti et al., 1995 (163)	20	13	4 (30.8)
Maccabruni et al., 1995 (162)	32	32	14 (43.7)
Thomas, 1998 (175)	162	145	13 (8.9)
Zanetti et al., 1995 (164)	40	36	9 (25)
Totals	355	275 (77.5)	65 (20.4)

TABLE 9.16. RISK OF VERTICAL TRANSMISSION OF HCV IN HIV-POSITIVE HCV-RNA–POSITIVE PREGNANT WOMEN

The finding that HIV-infected women transmitted HCV to their infants more frequently was thought to be the result of a higher level of maternal HCV viremia (114). Although studies have demonstrated a correlation between the risk of vertical transmission and maternal viremia with a titer level of more than 10^6 copies per milliliter (143,165,168), a specific cutoff value that predicts transmission has not been identified (114,175,176,177 and 178).

Recently, the conclusions from the International Consensus Conference on hepatitis C related to vertical transmission of HCV were summarized (164). This report noted that (a) the rate of vertical transmission of HCV is approximately 5% in unselected HIV-negative mothers but higher in HIV-HCV coinfected mothers; (b) vertical transmission is restricted to infants whose mothers are viremic and the risk of

transmission increases as maternal viral load increases, but a specific cutoff value that predicts transmission does not exist; (c) any association between maternal specific genotypes of HCV and vertical transmission remains unclear; (d) chronic liver disease and elevated ALT level are not risk factors for vertical transmission; (e) there is no difference in the risk of vertical transmission between infants delivered vaginally or by cesarean; and (f) there is no evidence demonstrating an increased risk of HCV in breast-fed infants. Although HCV RNA has been isolated from the colostrum and breast milk (169,176,177,178,179,180 and 181), the amount of HCV RNA present is too low to infect the newborn, the small amount of HCV in milk is easily inactivated by gastric juices, or the integrity of the oral and gastrointestinal tract mucosa effectively precludes HCV infection via the oral route (114). Neither the CDC nor the American Academy of Pediatrics recommends that HCV-infected mothers should not breast-feed to prevent HCV transmission (113,182). In addition, no association has been demonstrated between perinatal transmission of HCV and gestational age, duration of ruptured membranes, use of fetal scalp electrode, or chorioamnionitis (114).

HCV antibodies cross the placenta and may persist for up to 18 months in infants born to mothers who are HCV seropositive. Thus, diagnosis of HCV infection in infants younger than 18 months relies on testing for HCV RNA. After 18 months, screening for anti-HCV can be relied on. Approximately 70% of vertically infected infants test positive on polymerase chain reaction (PCR) for HCV RNA by 1 month of age; and 90%, by 3 months (164a). As in adults, most acute HCV infections in children progress to chronic disease (164a).

Prophylactic treatment of HCV-exposed neonates with HBIG does not reduce the risk of vertical transmission (114). Thus, passive immunization of neonates is not recommended. The high mutation rate of HCV and the resultant marked heterogeneity of HCV make development of an effective vaccine unlikely.

Diagnosis

After the discovery of the HCV genome by Choo et al. (107) in 1989, a number of assays have been developed for the detection and assessment of hepatitis C status (183). Generally these tests can be divided into serologic assays or virologic tests for HCV RNA. As noted by Gretch (184), serologic tests identify the presence of anti-HCV, which indicates exposure to HCV but does not differentiate among acute disease, resolved disease, or chronic HCV infection (184). Moreover, the presence of anti-HCV indicates HCV infection, not immunity (105). The virologic tests detect specific viral nucleic acid (HCV RNA) sequences, which are indicative of ongoing presence of HCV (183). In addition, viral detection is useful for retesting patients with false-negative antibody test results in whom HCV infection is suspected, determining whether a patient is viremic before instituting treatment, or determining the response of HCV infection to treatment (183).

The laboratory diagnosis of HCV infection is based principally on detection of anti-HCV. The anti-HCV assay is an enzyme immunoassay (EIA), which is inexpensive, easy to perform and relatively reliable (105). Since Kuo et al.(108) introduced an assay that measured antibodies to recombinant HCV peptides, three generations of EIAs have been developed, each with increasing sensitivity (183). Each generation included additional or reconfigured recombinant antigens. The sensitivity of the third-generation EIA for detection of anti-HCV is 97%, and it can

detect anti-HCV within 6 to 8 weeks of exposure (185,186). However, the specificity of the test is dependent on the population tested. For example, in a high-prevalence group (e.g., intravenous drug abuser with elevated ALT level), the positive predictive value is 90% to 95%. It has been suggested that because the accuracy of third-generation EIA tests are very good in high-prevalence populations, supplemental anti-HCV tests may not be necessary in high-risk populations (187). On the other hand, in a low-risk population (e.g., voluntary blood donors) the false-positive rate is as high as 50% to 60% (183).

Because of the low specificity in low-risk patients of even the third-generation EIA, a confirmatory test is necessary to evaluate positive EIA results. For HCV, the confirmatory test is the recombinant immunoblot assay (RIBA). This supplemental test has also evolved through three generations of assays. The RIBA identifies the specific HCV antigens to which antibodies are reacting in the EIA and thus is more specific than the EIA (105,188). A positive test result is the presence of two or more antigens, and an indeterminate result is the presence of one antigen (105). The third-generation RIBA tests reduce the frequency of indeterminate results (105). The RIBA confirms EIA-positive results in 40% of patients in low-risk populations and up to 80% in high-risk groups (114). In addition, there is a high correlation between a positive RIBA test result and the presence of HCV RNA (105,187,188).

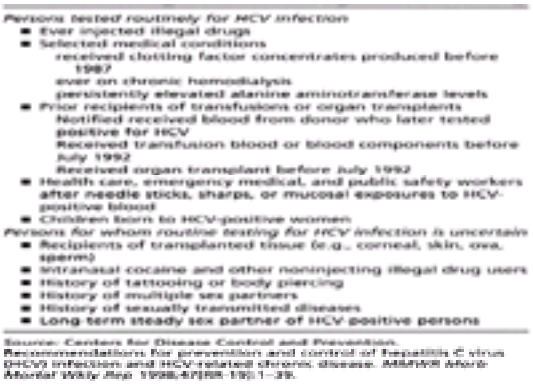
There are basically two types of tests to detect HCV RNA in plasma and serum: reverse transcriptase PCR (RT-PCR) and branched DNA (bDNA) assays (105,187,188). The bDNA assay (Quantiplex HCV RNA assay, Chiron Corp, Emeryville, CA) is a direct hybridization assay that uses a branch-chained DNA probe and amplification of the hybridization signal. Generally RT-PCR assays are more sensitive than the bDNA assay (105). The direct molecular qualitative detection of HCV RNA by RT-PCR is considered the gold standard for the diagnosis of HCV infection.

Development of the RT-PCR has significantly augmented the diagnostic capabilities related to HCV infection (187,188,189 and 190). This assay detects minute amounts of HCV RNA in blood and tissues and is used to document patients who are viremic. PCR can be used to demonstrate viremia in patients with chronic hepatitis C, to detect vertical perinatal transmission, and to improve the accuracy of blood bank screening for HCV infection (40). Lau et al. (190) reported on the use of a quantitative PCR assay for HCV. Assays that quantitate the titer level of HCV RNA include quantitative PCR (Amplicor HCV Monitor, Roche Molecular Systems, Nutley, NJ; HCV Superquant assay, National Genetics Institute, Culver City, CA) and bDNA assay (187). The principal advantage of quantitative PCR is their high sensitivity, although they have high assay variability with more than 1 million RNA copies (187). Quantitation of HCV RNA levels may prove useful in guiding therapeutic interventions (187). On the other hand, the bDNA assay is more standardized, but its sensitivity is limited (105). There is great variation among different quantitative assays, so it is important to use the same test performed by the same laboratory when obtaining serial measurements of viral titer levels (105).

An algorithm for use in the diagnosis of HCV infection is depicted in Fig. 9.5 (187). Table 9.17 lists the persons who should be screened for HCV infection. In addition, volunteer blood donors must be routinely screened for the presence of HCV. Patients with elevated aminotransferase levels, persons at risk for HCV infection (Table 9.16), and volunteer blood donors are screened with a third-generation EIA. In low-risk

patients, a positive EIA result is confirmed with the RIBA. For high-risk patients, HCV RNA testing should be performed. If HCV RNA is detected, a liver biopsy is usually done to assess disease severity (105,187). Unfortunately, serum aminotransferase level, HCV RNA level, or HCV genotype does not correlate well with the severity of liver disease (105,187). Because of improved treatment outcomes (see the Treatment section), it has been suggested that it is more cost effective to treat all HCV-infected patients without contraindications and perform biopsies only on those without sustained responses (105). Recently, two noninvasive markers of fibrosis or cirrhosis have been shown to be useful in predicting development of chronic liver disease (187). Serum hyaluronic acid concentration can be used to monitor patients at risk for progressive fibrosis and as a surrogate measure of antifibrogenic response in patients who cannot undergo liver biopsy (191). Cirrhosis has been accurately predicted in more than 90% of patients with chronic liver disease with the use of serum hyaluronic acid concentration (192). Serum type III procollagen peptide concentration has also been shown to predict development of chronic liver disease; levels correlate directly with severity of hepatis histology and inversely with response to therapy (193).

FIGURE 9.5. Algorithm for diagnosis of hepatitis C infection. EIA, enzyme immunoassay; RIBA, recombinant immunoblot assay; ALT, alanine aminotransferase; AST, aspartate aminotransferase. (From Thomas DL, Lemon SM. Hepatitis. In: Mandel GL, Bennett JE, Dolm R, eds. *Principles and practice of infectious diseases.* New York: Churchill Livingstone, 2000:1736–1760; and Schiff ER, Medina MD, Kahn RS. New perspectives in the diagnosis of hepatitis C. *Semin Liver Dis* 1999;19:3–15, with permission.)


Persons tested routinely for HCV infection
- Ever injected illegal drugs
- Selected medical conditions
  - received clotting factor concentrates produced before 1987
  - ever on chronic hemodialysis
  - persistently elevated alanine aminotransferase levels
- Prior recipients of transfusions or organ transplants
  - Notified received blood from donor who later tested positive for HCV
  - Received transfusion blood or blood components before July 1992
  - Received organ transplant before July 1992
- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to HCV-positive women

Persons for whom routine testing for HCV infection is uncertain
- Recipients of transplanted tissue (e.g., corneal, skin, ova, sperm)
- Intranasal cocaine and other noninjecting illegal drug users
- History of tattooing or body piercing
- History of multiple sex partners
- History of sexually transmitted diseases
- Long-term steady sex partner of HCV-positive persons

Source: Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47(RR-19):1–39.

TABLE 9.17. PERSONS IN WHOM SCREENING FOR HEPATITIS C VIRUS (HCV) INFECTION SHOULD BE UNDERTAKEN

Obstetrician-gynecologists and other providers of health care to women can play an important role in reducing the morbidity and mortality rates associated with chronic hepatitis C by screening high-risk patients with the characteristics noted in Table 9.17 (114). As a result of identifying asymptomatic women with chronic HCV infection, early diagnosis of HCV in their infants and institution of treatment (see the Treatment section) in the women or their infants may prevent the serious complications associated with chronic HCV infection (114).

Treatment

There is no effective treatment for acute HCV infection and only supportive therapy is available. Management of chronic HCV infection is complicated by its rapid mutation rate and lack of neutralizing antibody to viral agents. INF-a and ribavirin therapy are the only treatments available for chronic HCV infection that have been shown to be effective (105,112,113 and 114,194,195 and 196). However, sustained response rates (normal serum aminotransferase levels or undetectable HCV RNA 6 months after completing treatment) occur in less than half of the patients (195).

Until recently, INF-a was the only available therapy for chronic hepatitis C. INF-a in the standard dosage of 3 million units subcutaneously three times a week for 6 months results in biochemical (normalization of aminotransferase levels) responses in approximately 40% of patients and virologic responses in 30% to 40% (112). However, improvement in many instances is transient with sustained responses of 15% to 20% and 10% to 15% occurring biochemically and virologically, respectively (112,197,198 and 199). A sustained biochemical and virologic response with histologic improvement on liver biopsy occurs in 7% to 20% of patients (197,198 and 199).

Increasing the duration of treatment with interferon alone to 1 year increases the sustained response rate to 20% to 25% (112). In the metaanalysis by Carithers and Emerson (198) summarizing 20 randomized, controlled trials, extending the duration of therapy to 12 to 24 months produced a sustained response rate of 27%, compared with only 14% for a 6-month course ($p < 0.001$). Thus, extended-duration interferon therapy is the standard of care for the treatment of chronic hepatitis C when interferon monotherapy is used (200).

Recent clinical trials in the United States and Europe demonstrated that combination therapy with INF-a-2b plus ribavirin (a nucleoside analog) resulted in an approximate doubling to 40% of the response rate, compared with standard monotherapy with interferon (201,202). Ribavirin is typically given orally (1,000 to 1,200 mg per day). The major side effect of ribavirin is a dose-dependent hemolytic anemia, which is reversible (195). In patients who relapse after treatment with interferon alone, combination therapy with interferon and ribavirin results in higher rates of sustained virologic, biochemical, and histologic response than treatment with interferon alone

(203). In the study by Davis et al. (203), HCV RNA levels were undetectable 24 weeks posttherapy in 49% of the combination therapy group, compared with 5% in the interferon alone group ($p < 0.001$). Thus, currently, combination therapy with interferon and ribavirin is considered first-line therapy for initial treatment and relapse treatment in patients with chronic hepatitis C (195,196).

Future therapies for chronic hepatitis C include (a) induction interferon therapy using 10 to 15 million units of INF-a daily (204,205); (b) a long-acting formulation of interferon conjugated with polyethylene glycol administered once a week subcutaneously, which produced a sustained virologic response rate equivalent to that seen with combination interferon and ribavirin (195); (c) inhibition of viral replication by the use of enzyme inhibitors to HCV protease, helicase, or replicase (206); and (d) inhibition of viral replication using antisense oligonucleotides, ribozymes that catalyze cleavage of HCV RNA, or gene transfer of interfering proteins that interrupt virion assembly in the hepatocyte (195).

Prevention

Routine screening of pregnant women for HCV is not currently recommended. However, clinicians might wish to screen high-risk populations as noted in Table 9.17. Patients who are seropositive for HCV should be assessed for liver enzymes. If transaminase levels are elevated, consultation with a hepatologist or gastroenterologist is indicated. If the levels are within the normal reference range, they should be repeated in 6 to 12 months. After a seropositive mother has delivered a baby, the pediatrician should be apprised of the mother's seropositivity so follow-up of the baby can be instituted.

No active immunization with vaccination is available for HCV. In the past, conflicting data existed as to the efficacy of pooled human Ig in modifying or preventing HCV infection (105). However, HCV-seropositive donations are no longer included in the plasma pool from which Ig is manufactured; thus, no benefit would accrue from products currently on the market (105). Therefore, administration of Ig is not recommended after exposure to HCV (113). Health care workers with percutaneous exposure to HCV should be screened for anti-HCV and have an ALT test as soon as possible after exposure to exclude prior infection. Serologic and ALT testing should be repeated at least once, 6 months later. It has also been suggested that HCV RNA be tested for 2 to 4 weeks after exposure because treatment of HCV (interferon or interferon plus ribavirin) may be more effective early in the course of infection (104). However, this is not well established.

The key to prevention of HCV infection is decreasing exposure to contaminated blood (105). Universal screening of blood donors for anti-HCV and surrogate markers of HCV infection has virtually eliminated (1 per 100,000 units of blood) the risk of posttransfusion HCV infection (112,113). In addition, HCV-infected persons are counseled to not donate blood, organs, tissue, or semen (194). Transmission rates of HCV in high-risk groups can be reduced by public health policies such as needle-exchange programs and promotion of safe sex (i.e., condom use). Whether condom use is beneficial for persons in a steady monogamous relationship has not been demonstrated (194). HCV infection is not a contraindication for pregnancy. Infants born to HCV-seropositive women should be screened for HCV RNA.

Adherence to universal precautions minimizes the risk for HCV transmission to

health care workers. Prophylaxis with Ig post–needle stick exposure is not effective and is currently not recommended (113). Nosocomial HCV transmission is the major source of HCV infection in developing countries. As universal precautions are increasingly practiced in these countries, the nosocomial transmission rate of HCV should decrease (105). Alcohol has been demonstrated to be a risk factor for exacerbation and progression of chronic HCV infection (207). Thus, abstinence should be recommended for HCV-infected persons.

HEPATITIS D (DELTA VIRUS)

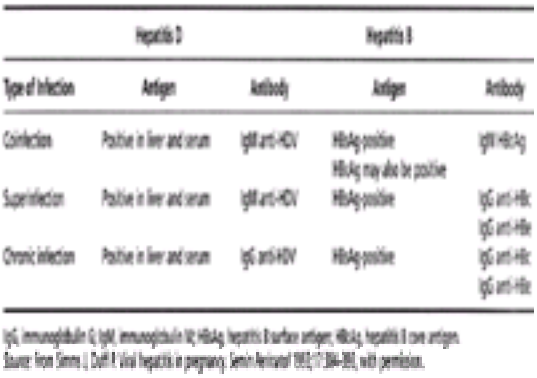
The delta agent is an incomplete RNA virus that requires HBsAg for replication and thus is considered a defective virus. Hepatitis D has an external coat of HBsAg and an internal delta agent encoded by its own genome. Because the delta agent can only replicate and cause hepatitis in the presence of active HBV infection (clinical or subclinical), it can be acquired as a primary infection concomitantly with HBV or as a superinfection in an established HBV carrier (208,209).

The epidemiology of hepatitis D is virtually identical to that of hepatitis B (217). Two distinct epidemiologic patterns have been described for HDV infection. In Mediterranean countries (southern Europe, the Middle East, and northern Africa), HDV infection is endemic among persons infected with HBV, and most infections are thought to be transmitted by intimate contact. HDV may play a prominent role in chronic liver disease in endemic areas (e.g., Italy) where 32% of HBsAg carriers with chronic active hepatitis and 52% with cirrhosis are delta-antigen positive, although delta antigen was not detected in HBsAg carriers with no liver disease (210,211). In nonendemic areas such as North America and northern Europe, HDV infection is generally found in people exposed frequently to blood and blood products.

In the United States, HDV infection occurs most commonly in parenteral drug abusers (42,63). In addition, HDV infection has been reported in other groups that are at increased risk for HBV infection such as hemophiliacs, homosexual men, health care workers, patients undergoing hemodialysis, transfusion recipients, immigrants from high-prevalence HBV areas, and institutionalized patients (42,63,212). Perinatal transmission of HDV has been reported (213). Lettau et al. (63) demonstrated that heterosexual contacts of patients infected with HBV and HDV are also at risk for HDV infection.

Because HDV infection requires concomitant HBV infection, it can occur in three forms (Table 9.18): (a) an acute simultaneous HDV and HBV infection (coinfection), (b) an acute HDV infection superimposed on a chronic HBV infection (superinfection), and (c) a chronic HDV infection superimposed on a chronic HBV infection. Hoofnagle (215) has suggested that the most common situation is acute HDV infection that is superimposed on a chronic HBsAg carrier. As noted by Nishioka and Dienstag (209) and Shattuck et al. (214), the most disturbing feature of HDV is its propensity for contributing to severe or fulminant HBV infection. HDV is strongly associated with fulminant hepatitis. For example, in an outbreak of severe hepatitis among intravenous drug abusers, 91% of patients with fulminant hepatitis had delta infection (63). In addition, HDV superinfection can transform asymptomatic or mild chronic HBV infection to severe, progressive chronic active hepatitis and cirrhosis and accelerate the course of chronic active hepatitis. Approximately 20% to 25% of patients with chronic hepatitis B ultimately become superinfected with hepatitis D and 80% of these individuals subsequently develop chronic hepatitis

(208,215,216,217,218,219 and 220).



	Hepatitis D		Hepatitis B	
Type of Infection	Antigen	Antibody	Antigen	Antibody
Coinfection	Positive in liver and serum	IgM anti-HDV	HBsAg positive HBcAg may also be positive	IgM anti-HBcAg
Superinfection	Positive in liver and serum	IgM anti-HDV	HBsAg positive	IgG anti-HBc IgG anti-HBe
Chronic infection	Positive in liver and serum	IgG anti-HDV	HBsAg positive	IgG anti-HBc IgG anti-HBe

IgG, immunoglobulin G; IgM, immunoglobulin M; HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen.
Source: From Simmons J, Duff P. Viral hepatitis in pregnancy. Semin Perinatol 1993;17:384–393, with permission.

TABLE 9.18. DIAGNOSIS OF THE DIFFERENT FORMS OF HEPATITIS D INFECTION

The clinical presentation of acute hepatitis D is similar to that of the other forms of acute viral hepatitis, as described in detail in the section on hepatitis A. Perinatal transmission of HDV has been demonstrated by Zanetti et al. (213). However, perinatal transmission with hepatitis D is rare because immunoprophylaxis of the neonate against hepatitis B is nearly 100% effective in preventing hepatitis D (221). HDV antigen can be detected early in the acute infection, and antibody to delta antigen can be detected after recovery.

The diagnosis of acute coinfection is confirmed by detecting delta antigen in either hepatitis tissue or hepatitis serum and IgM-specific antibody in serum with concomitant evidence of acute hepatitis B (HBsAg and IgM anti-HBc positive) (Table 9.18). With superinfection, the serologic tests will confirm acute hepatitis D (antibody to HDV [anti-HDV] positive and IgM anti-HDV positive) and chronic hepatitis infection (HBsAg positive and IgM anti-HBcAg negative). In the face of chronic hepatitis D, the IgG anti-HDV level will be elevated, delta antigen will be present, and HBsAg will be present.

Management of acute hepatitis D is similar to that for the other forms of acute viral hepatitis and consists generally of supportive care (see description in the section on hepatitis A). For patients with chronic infection, periodic monitoring should be undertaken for declining hepatic function or development of coagulopathy (102). No specific antiviral agent or immunotherapy is curative for either acute or chronic hepatitis D.

HEPATITIS E

The enterically transmitted form of non-A, non-B hepatitis is caused by HEV, an RNA virus whose epidemiology is similar to that of hepatitis A. Transmission is by the fecal-oral route. Hepatitis E has been demonstrated in many countries in Asia, Africa, the Middle East, Russia, Central America, and Mexico (222,223,224,225,226,227

and 228). HEV is a major cause of both epidemic and acute, sporadic hepatitis in many developing countries. A non-A, non-B enteric virus was suspected on epidemiologic grounds for more than a decade before isolation, cloning, and sequencing of HEV in the early 1990s (229). The disease occurs in epidemic and sporadic forms, with the epidemic form associated with more severe infection. Most outbreaks of HEV have been associated with gross contamination of drinking water with fecal material and have usually occurred during the rainy season or after flooding (222). Hepatitis E is rare in the United States and western Europe, where all cases have occurred in immigrants from or tourists returning from endemic areas.

The incubation period of HEV ranges from 15 to 60 days (mean, 40 days). During epidemics, the attack rate is highest among young adults in the 15- to 39-year old age-group. Thus, this disease can be expected to occur among pregnant women.

Although enterically transmitted HEV is transmitted in a similar manner to HAV, it is a much more severe disease (222). The major difference is the mortality rate. Whereas the case fatality among patients with HAV who are ill enough to be hospitalized is 1 to 2 per 1,000, in epidemics of hepatitis E, the overall case fatality rate is 1% to 2% (222). HEV was noted to be the cause of fulminant hepatitis in 62% of cases in a large study from India (230). In this study, one fourth of the women with fulminant hepatitis were pregnant. The most severe form of this disease occurs in pregnant women, particularly during the third trimester. Among this group of pregnant women, the case fatality rate is 10% to 20% (222,224,225,226 and 227,230). Extreme poverty, coexisting medical illnesses, malnutrition, and poor prenatal care are partially responsible for this poor maternal outcome (102,231). Although acute hepatitis E can be severe, it is a self-limiting disease without chronic liver disease or sequelae (232).

Because a chronic carrier state does not occur, the risk of vertical transmission of HEV from infected mother to infant was thought to be low (117). However, acute HEV infection during the third trimester has been demonstrated not only to result in vertical transmission of HEV but also to be associated with significant risk of morbidity and mortality for the neonate (233). Evidence of HEV infection was found in six (75%) of eight infants born to mothers with acute HEV infection during the third trimester (233). Two neonates developed hypothermia and hypoglycemia and died within 24 hours; massive hepatic necrosis was present in one of these infants. Four additional infants had hepatitis.

Clinically, acute hepatitis E presents similarly to all other forms of acute viral hepatitis. Until recently, the diagnosis of acute hepatitis E was based on clinical examination plus exclusion of other forms of hepatitis. There are now three diagnostic laboratory tests for the diagnosis of hepatitis E (Table 9.2). Virus-like particles can be identified in a stool specimen using electron microscopy. Antibody to HEV (anti-HEV) can be detected by immune electron microscopy, by inhibition of immunofluorescent detection of HEV antigen in hepatocyte cytoplasm, and by an EIA using antigen expressed in recombinant DNA systems (acute viral hepatitis). Currently, there is no vaccine against HEV and Ig has not been effective in preventing infection.

HEPATITIS G AND TTV

As described at the beginning of this chapter, several additional agents have been

identified as potential hepatitis viruses (1). These include HFV, GBV-C (i.e., HGV), and TTV. Although HFV was recovered from the feces of a patient with hepatitis, subsequent studies have not confirmed this finding and the role of HFV in acute hepatitis is uncertain (2).

HGV and GBV-C were initially described by two independent groups as separate viruses but are now considered a single agent (3,4). HGV is a single-stranded RNA virus that is distinct from HCV in that it lacks a core protein and hypervariable region in its envelope glycoproteins (1). HGV RNA has been detected with RT-PCR in various groups, suggesting that HGV can be transmitted by parenteral routes (234,235,236 and 237), sexual intercourse (238,239), and vertical transmission from mother to infant (240,241,242 and 243). As noted by Kawai and Feinstone (1), although some studies have detected HGV in cases of fulminant hepatitis, an etiologic role for HGV has not been demonstrated. In addition, studies in the United States have not demonstrated a significant correlation between infection with HGV and posttransfusion hepatitis (244) or sporadic hepatitis (245,246). HGV shares the same risk factors associated as those of HCV (1). However, coinfection with HGV does not influence the clinical features, liver histology, and response to therapy or risk for developing hepatocellular carcinoma in HCV-infected patients (1). Thus, HGV is generally regarded as a nonhepatitis virus that shares common pathways of transmission with hepatitis viruses, particularly HCV (247,248).

More recently, another new non–A-G “hepatitis” agent has been proposed. This agent is designated TTV and was identified in Japan from the serum of a patient with non–A-G posttransfusion hepatitis (5). In this initial study, three of five patients had posttransfusion hepatitis not associated with hepatitis A-G virus (5). Subsequently, TTV was detected in blood donors and blood products in the United Kingdom (249) and patients with liver disease (250). As with HGV, it remains unclear whether TTV is a primary hepatitis virus and whether it is responsible for cryptogenic cases of fulminant hepatitis, chronic hepatitis, or cirrhosis (251). There remains uncertainty about the etiologic role of TTV in acute hepatitis as well (1,251).

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10

HIV/AIDS

The acquired immunodeficiency syndrome (AIDS) initially was recognized as a separate disease in 1981 (1,2 and 3). Over the 2 decades since, AIDS has reached epidemic proportions. Through June 2000, there were 753,907 cases reported to the Centers for Disease Control and Prevention (CDC) in the United States (4). Of these reported cases, 8,804 were pediatric cases (age younger than 13 years). Among adult cases, 620,189 (83%) occurred in males and 124,911 (17%) in females. Through June 2000, 438,795 persons with AIDS died, leaving over 300,000 persons living with AIDS in the United States (4). From July 1999 to June 2000, a total of 43,293 adult/adolescent cases of AIDS were reported to the CDC: 32,824 (76%) male and 10,469 (24%) female (Table 10.1) (4). In the United States, over 80% of the cumulative cases of AIDS in women occurred among persons in the reproductive age group (4). Among the pediatric AIDS cases, 91% were secondary to mother-infant transmission (4).

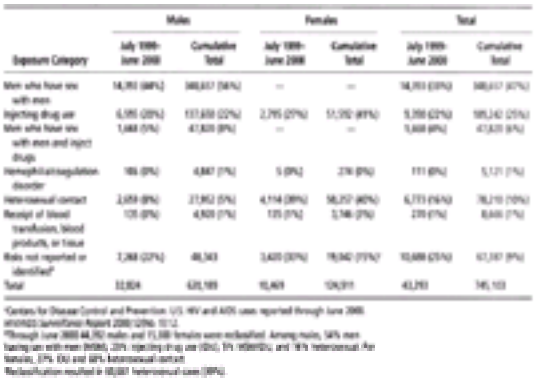


TABLE 10.1. ACQUIRED IMMUNODEFICIENCY SYNDROME CASES BY EXPOSURE CATEGORY AND SEX AMONG ADULTS AND ADOLESCENTS REPORTED IN THE UNITED STATES[a] THROUGH JUNE 2000

The annual AIDS rates per 100,000 population for cases reported from July 1999 to June 2000 by geographic area are shown in Fig. 10.1 and Fig. 10.2 (4). Overall, the rates per 100,000 population were 30.1 for males and 9.0 for females (4). Among the cases reported in 1999, the largest racial group were blacks (48%), followed by whites (30%), Hispanics (20%), and American-Indian/Alaskan Natives or Asian/Pacific Islanders (1%) (5). By HIV exposure category among male adults/adolescents, men having sex with men (MSM) remain the largest single group of persons reported with AIDS (44%) (Table 10.1) (4). Injecting drug use (IDU) was the second largest group (20%), followed by heterosexual contact (8%) and MSM plus IDU (5%) (4). A different pattern exists in women, in whom the largest group is heterosexual contact (39%), followed by IDU (27%) (4). Roughly two thirds of “not reported or identified” cases in women are reclassified as heterosexual upon further evaluation (4). Thus, heterosexual contact probably accounted for over 60% of AIDS cases reported in women from July 1999 to June 2000 (4). Geographic analysis by the CDC for 1997 to 1999 found the largest number of U.S. AIDS cases were reported from the South, followed by the Northeast (4).

FIGURE 10.1. Male adult/adolescents annual AIDS rate per 100,000 population, for cases reported from July 1999 to June 2000 in the United States

FIGURE 10.2. Female adult/adolescent annual AIDS rate per 100,000 population, for cases reported from July 1999 to June 2000 in the United States.

Reported cases of AIDS represent only the tip of the iceberg. An estimated 650,000 to 900,000 Americans are infected with the etiologic agent of AIDS, the human immunodeficiency virus (HIV) (6,7). By 1992, approximately 0.3% of U.S. residents were HIV infected, and an estimated 40,000 new HIV infections were occurring annually (6,7). Among men, 0.6% were HIV infected; non-Hispanic blacks 2% and Hispanics 1% (6,7). In women, 0.1% were HIV infected, 0.6% among non-Hispanic blacks (6,7).

Commencing in 1988, the CDC has conducted a national HIV surveillance system in populations at risk for HIV infection (8,9 and 10). These include sexually transmitted disease (STD) clinics (11,12 and 13), drug treatment centers (14,15 and 16), adolescents and adults in other clinical settings (17,18,19 and 20), and filter paper testing of newborns as a surrogate for childbearing women and children (21,22,23,24,25,26,27 and 28). Taken together, these surveys of seroprevalence demonstrated that by the late 1980s and early 1990s, HIV prevalence in U.S. men had stabilized and actually started to decline in some groups; in women the rates had stabilized (29). In MSM attending STD clinics, seroprevalence decreased less than 20% from 1990 to 1996, well below the median of 36% seen in 1988 (29). Among heterosexuals attending STD clinics, seroprevalence of HIV remained lower (median 1.7% in men and 1.2% women) and has been stable from 1990 to 1996 (Fig. 10.3).

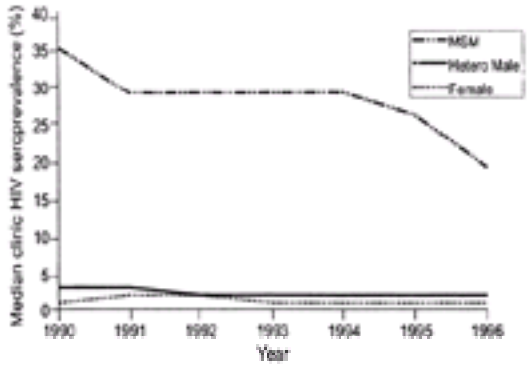


FIGURE 10.3. Trends in median HIV seroprevalence among persons attending STD clinics by selected HIV exposure mode and sex from 1990 to 1996. Female, heterosexual female; hetero male, heterosexual male; MSM, men who have sex with men.

In 1996, the median seroprevalence rate of HIV among IDUs entering drug treatment centers was 9.5% (29). In this group, infection is concentrated along the East Coast and in the South, with HIV seroprevalence rates in Baltimore (32.2%), New York City (28.5%), and Atlanta (25%) substantially higher than those seen in San Francisco (1.6%) and Los Angeles (1.5%) (29). These differences probably can be explained by the frequency of sharing injecting equipment, the number of needle-sharing partners, and the use of “shooting galleries” (29). As shown in Fig. 10.4, seroprevalence declined in the Northeast from 1990 to 1996, whereas it increased in the South to a level higher than that in the Northeast.

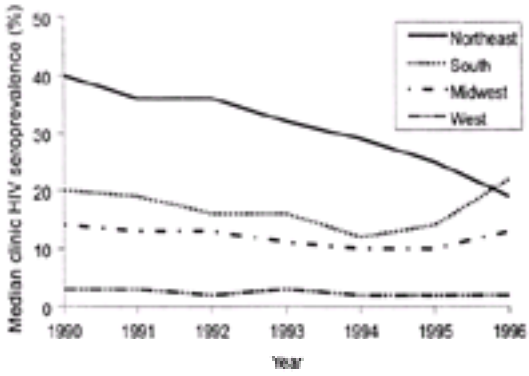


FIGURE 10.4. Trends in median HIV seroprevalence among injection drug users.

From 1989 to 1994, the CDC surveyed HIV seroprevalence in childbearing women (30). As of 1994, seroprevalence was 0.15% among childbearing women, and the geographic distribution was similar to that of IDUs (highest along the Atlantic Coast and in the South) (Fig. 10.5). The highest seroprevalence rates among these women

were in Washington, DC (6.9/1,000), New York (5.2/1,000), and Florida (4.6/1,000). As in other groups, the HIV seroprevalence rate among childbearing women remains considerably higher in racial and ethnic minority populations (29).

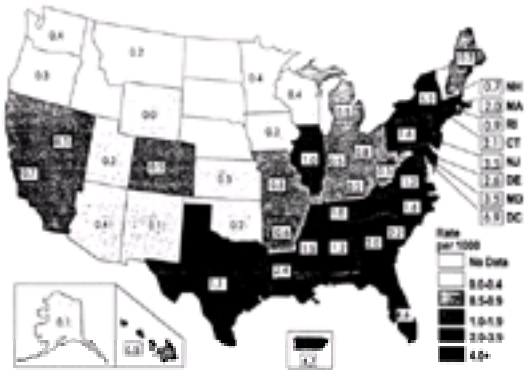


FIGURE 10.5. Prevalence of HIV infection in childbearing women in the United States, 1994.

It is important to recognize that the HIV epidemic in the United States exists in the context of a much larger (and perhaps more devastating) global pandemic of HIV infection and AIDS, with cases reported to the World Health Organization from virtually every country (31). The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that by the end of 1999, a total of 53.1 million adults and children worldwide had been infected with HIV (32). Approximately 18.8 million (35%) of these persons have already died from AIDS, and 34.3 million are currently living with HIV infection. Of these HIV-infected persons, over 90% live in developing countries (Table 10.2). UNAIDS estimates that during 1999, more than five million persons were newly infected with HIV (4.7 million adults and 620,000 children) (32). Of these, almost all lived in developing countries.

People with HIV or AIDS	Regional Total
Developing world	
Sub-Saharan Africa	24.5 million
South and Southeast Asia	5.6 million
Latin America	1.3 million
East Asia and Pacific	530,000
Caribbean	360,000
Eastern Europe and Central Asia	420,000
North African and Middle East	220,000
Industrialized world	
North America	900,000
Western Europe	520,000
Australia and New Zealand	15,000

From UNAIDS. *Report on the global HIV/AIDS epidemic: June 2000.* Geneva: World Health Organization, 2000.
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

TABLE 10.2. ESTIMATED NUMBER OF PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME WORLDWIDE AS OF DECEMBER 1999

In the developing world, most adult transmission occurs as the result of heterosexual sex (32). Parenteral transmission by sharing unsterilized needles and syringes among IDUs is the second most common mode of transmission; this is particularly prominent in Asia, Eastern Europe, and South America (32). Mother-infant (perinatal) transmission is third; this mode is common in sub-Saharan Africa, where it is responsible for 15% to 20% of HIV infections (33). In other regions of the developing world, perinatal transmission accounts for 5% to 10% of HIV infections (34). Other routes of transmission in developing countries include blood transfusion (<10%) and medical injection with contaminated needles (<5%) (35).

Globally, HIV infection has had a major adverse impact on health and life expectancy (36). In developing countries, AIDS causes a large proportion of mortality. Through the end of 1999, UNAIDS estimated that 12.7 million adults and 3.6 million children had died of AIDS since the epidemic began (32). In the last decade of the twentieth century, AIDS was the third leading cause of death in adults in developing countries (after tuberculosis and other infections), and its share of mortality grew faster than any other cause (37). In the sub-Saharan African countries with the severest epidemics, over 50% of adult mortality is attributable to HIV infection (38). Similarly, infant mortality rates in developing countries are higher due to AIDS (38). Stanecki and Way (39) have projected that by 2010, the infant mortality rate in Zimbabwe will be double what it would have been without AIDS. As a result of the increased mortality rates, the HIV epidemic has significantly reduced the life expectancy rates in many developing countries, eradicating the hard-earned gains these countries achieved over the past 20 to 30 years (36). In Botswana and Zimbabwe where the epidemic has been severe, life expectancy has been reduced 32 years (40).

During the last decade, we have seen the emergence of parallel epidemics (41). As reviewed by Mayer (41), the recent advances in our understanding of the natural history of the immunodeficiency associated with HIV infection and the development of highly active antiretroviral therapy (HAART) have led to dramatic decreases in mortality and morbidity in persons with access to diagnostic monitoring (viral load, CD4 counts) and HAART (Fig. 10.6). Thus, in industrialized countries, management has changed from a focus on treating opportunistic infections and caring for the dying to a focus on compliance and quality of life (41). Unfortunately, in both the developing world and disadvantaged communities in industrialized countries, the HIV epidemic continues to weave its pattern of mortality and morbidity.

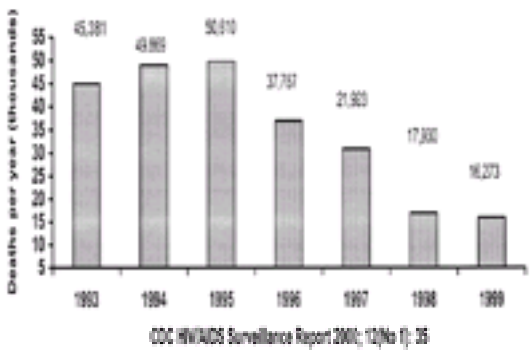


FIGURE 10.6. Estimated deaths of persons with AIDS by year of death, from 1993 to 1999 in the United States.

Whereas women overall represent only 17% of all cumulative reported AIDS patients through June 2000, the number of AIDS cases in women has been increasing steadily each year (Fig. 10.7). The increasing presence of women in the AIDS epidemic in the United States is clearly demonstrated by comparing the prevalence of women among the first 100,000 reported cases of AIDS (9%) and the 12 months from July 1999 to June 2000 (24%) (4,42). Whereas cases in men still account for the large majority of AIDS cases, reported cases in women are increasing more rapidly (4,43,44 and 45). Not only do women account for an increasing proportion of reported cases of AIDS (46), but AIDS has been among the leading causes of death in U.S. women of reproductive age since 1992 (47). AIDS is now the third leading cause of death in all women and the leading cause of death in African-American women (48).

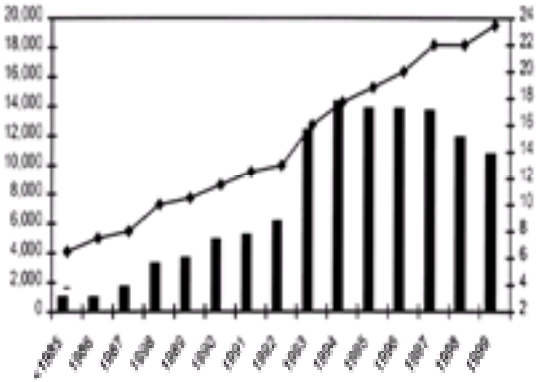


FIGURE 10.7. Women with AIDS. Incidence and percentage of adult AIDS cases by year, from 1981 to 2000.

Globally, a similar pattern has emerged. More men have been infected with HIV than women (except in sub-Saharan Africa), but new infections are increasing more rapidly in women (36). These gender differences are explained by a variety of biologic, behavioral, and social factors, which include (i) HIV is more easily transmitted from men to women (49); (ii) young women and girls are more susceptible to infection due to a greater degree of cervicovaginal fragility than is seen in older women; (iii) women are more likely than men to have asymptomatic STDs, which are more likely to go untreated, resulting in an increased risk for acquisition of HIV; and (iv) social factors in which women lack control over conditions under which they have sex (e.g., lack of condom use). The AIDS epidemic has had its greatest impact on minority populations in the United States, particularly among African-Americans and Hispanics. The rates of AIDS in these groups are three to four times greater than those in whites. Among women, this racial/ethnic disparity is

strikingly magnified.

This rising rate of HIV infection in women mandates that providers of health care to women in the United States play an increasing role in the effort to meet the challenge of the AIDS epidemic. Specifically, providers of health care to women will need to provide care not only to HIV-infected pregnant women but also to HIV-infected nonpregnant women. They need to become actively involved in the efforts to control the spread of HIV (50). In addition, obstetrician-gynecologists must be able to provide appropriate counseling and medical care for these women.

As described by Minkoff (51), the picture of the U.S. AIDS epidemic in the new millennium is very different from that seen when the epidemic emerged in the 1980s. The race and gender of the HIV-infected population are increasingly minority (African-American and Hispanic), female, and in the reproductive age group. Haverkos and Chung (52) compared the number of cases reported each year according to sex, race or ethnic group, and category of exposure (Table 10.3). Men having sex with men (including IDUs) make up the largest group each year, but they are decreasing as a proportion from 62% in 1989, 48% in 1994, and 37% in 1999. The groups with the largest percentage increases over time were the heterosexual group and the group without risk factors reported or identified. Many of the latter, especially among females, are ultimately reclassified as heterosexual (4). Table 10.3 lists the increasing percentage of women, members of racial or ethnic minorities, and AIDS patients infected through heterosexual contact (53). Introduction of new, more effective antiretroviral agents that will result in longer, healthier lives for HIV-infected persons and the new demographic profile of the epidemic suggest that HIV infection among pregnant and nonpregnant women will continue to be a challenge for women's health care providers (51).

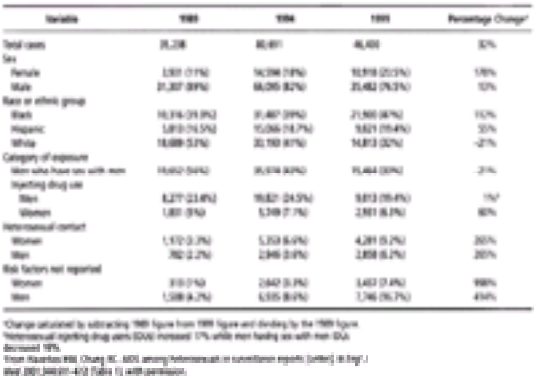


TABLE 10.3. CASES OF ACQUIRED IMMUNODEFICIENCY SYNDROME REPORTED IN THE UNITED STATES IN 1989, 1994, AND 1999, ACCORDING TO SEX, RACE, OR ETHNIC GROUP, AND CATEGORY OF EXPOSURE[c]

Other important trends in the AIDS epidemic have occurred in the United States (29). In the early 1990s, the annual incidence of AIDS-related opportunistic infections increased approximately 2% (29). However, in 1996, for the first time, AIDS-related opportunistic infections declined 6% compared to 1995 (Fig. 10.8) (54). Deaths

among AIDS cases also have been declining (29). Whereas from 1993 to 1995 HIV infection was the leading cause of death in the United States in the 25- to 44-year-old age group, in 1996 HIV-associated deaths declined 23% and fell to second place (Fig. 10.9) (54). These declines in AIDS-related opportunistic infections and deaths reflect, to a large extent, the impact of antiretroviral therapies, prophylaxis against AIDS-related opportunistic infections, and efforts at HIV prevention (29).

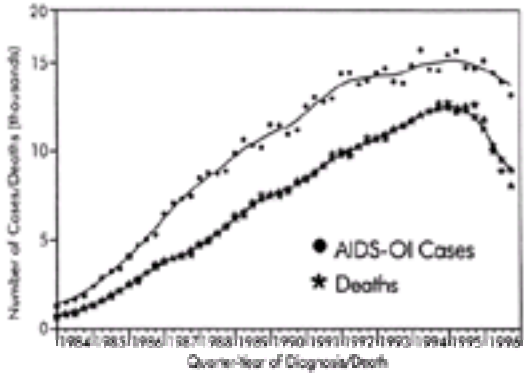


FIGURE 10.8. Estimated incidence of AIDS-related opportunistic illnesses and estimated deaths among persons with AIDS.

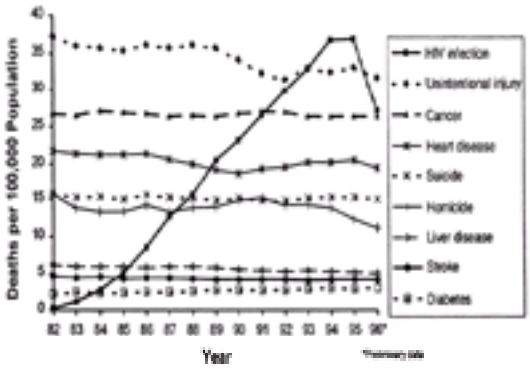


FIGURE 10.9. Trends in rates of death from leading causes of death among persons 25 to 44 years old in the United States from 1982 to 1996.

The most dramatic favorable trend of the AIDS epidemic in the United States has been the decline in perinatally acquired AIDS (Fig. 10.10) (5,29,51). From the peak in 1992, the estimated number of children with perinatally acquired AIDS has declined over 75% (5). This tremendous accomplishment followed publication of CDC guidelines for use of zidovudine (ZDV) to reduce perinatal transmission of HIV in 1994 (55) and for universal HIV counseling and voluntary testing of pregnant women

in 1995 (56).

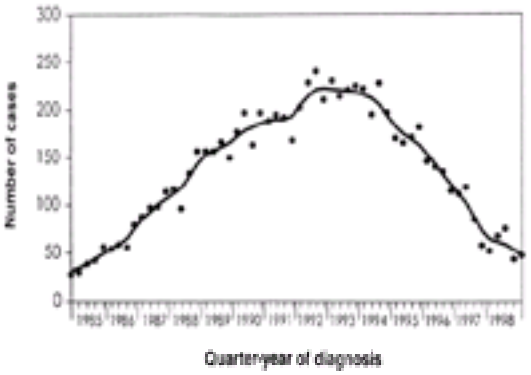


FIGURE 10.10. Perinatally acquired AIDS, from 1985 to 1998 in the United States.

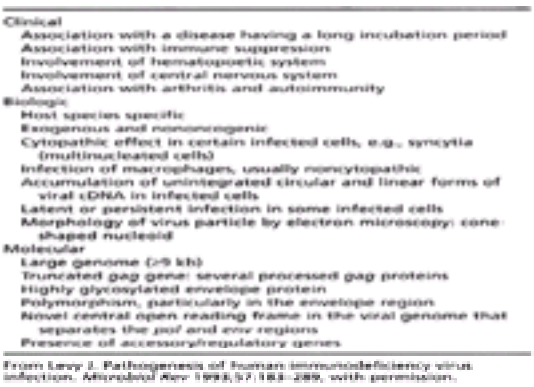
Etiology And Pathogenesis

Acquired immunodeficiency syndrome is caused by infection with HIV (55). Two types of HIV that are able to cause AIDS in humans have been identified: type 1 (HIV-1) and type 2 (HIV-2) (55). Human immunodeficiency virus type 1 is substantially more common than type 2. A large number of epidemiologic and virologic studies have confirmed conclusively that HIV is the etiologic agent of AIDS and have shown that the major routes of HIV infection are by blood and/or blood products, intimate sexual contact, and perinatal transmission from infected mothers (56).

Based on its characteristic dense, cylindrical, nucleoid-containing core proteins, genomic RNA, and the reverse transcriptase (RT) enzyme, HIV is classified as a member of the retrovirus family (57,58 and 59). All members of the retrovirus family code for the RT enzyme (RNA-dependent DNA polymerase), which allows the viral RNA to be transcribed into a DNA copy. It then integrates into the genome of the infected cell and replicates via the proviral DNA (56,57,58,59 and 60). There are seven distinct genera of retroviruses (59). Three of the retrovirus genera are pathogenic in humans: (i) lentiviruses, which include HIV-1 and HIV-2; (ii) the BLV-HTVL (bovine leukemia virus–human T-cell lymphoma/leukemia virus) genus, which includes human foamy virus; and (iv) a new human retrovirus related to type B and type D retroviruses (59).

Human immunodeficiency virus is a member of the lentivirus subfamily of human retroviruses (57,59). The lentivirus subfamily contains several animal viruses, including visna virus, maedi virus, the caprine arthritis-encephalitis virus, equine infectious anemia virus, bovine lentivirus, feline leukemia virus, and simian AIDS virus (SIV). Human immunodeficiency virus shares a variety of characteristics with other lentiviruses (Table 10.4). The lentiviruses characteristically result in chronic indolent infections with involvement of the nervous system, long periods of clinical latency, and weak humoral immune responses complicated by persistent viremia

(59,60,61 and 62).



Clinical
Association with a disease having a long incubation period
Association with immune suppression
Involvement of hematopoietic system
Involvement of central nervous system
Association with arthritis and autoimmunity
Biologic
Host species specific
Exogenous and nononcogenic
Cytopathic effect in certain infected cells, e.g., syncytia (multinucleated cells)
Infection of macrophages, usually noncytopathic
Accumulation of unintegrated circular and linear forms of viral cDNA in infected cells
Latent or persistent infection in some infected cells
Morphology of virus particle by electron microscopy: cone-shaped nucleoid
Molecular
Large genome (>9 kb)
Truncated gag gene: several processed gag proteins
Highly glycosylated envelope protein
Polymorphism, particularly in the envelope region
Novel central open reading frame in the viral genome that separates the *pol* and *env* regions
Presence of accessory/regulatory genes

From Levy J. Pathogenesis of human immunodeficiency virus infection. Microbiol Rev 1993;57:183–289, with permission.

TABLE 10.4. CHARACTERISTICS COMMON TO LENTIVIRUSES

In 1987, a new subgroup of HIV retroviruses was recovered from West African AIDS patients (63). This subtype, named HIV-2, is clearly associated with immunodeficiency and a clinical syndrome similar to AIDS (57). As noted by Levy (61), although antibodies to HIV-2 have been found primarily in individuals from West Africa, individuals from Europe, South America, and, most recently, the United States have been identified with HIV-2 antibodies. Evans and coworkers (64) have demonstrated that individuals may be simultaneously infected by HIV-1 and HIV-2.

HIV Type 1 Virion and Genomic Structure

The structure of HIV is depicted schematically in Fig. 10.11. The HIV virion has a diameter of approximately 100 nm and contains a lipid bilayer envelope that surrounds a cone-shaped core composed of the viral p24 Gag protein. Inside this capsid are two identical RNA stands with which RT and the nucleocapsid proteins p9 and p6 are closely associated (59,60 and 61). The inner portion of the viral membrane is surrounded by the p17 core (Gag) protein, which provides the matrix (MA) for the viral structure and is vital to the virion's integrity (59,60 and 61). The viral surface is made up of 72 knobs of the envelope glycoproteins, including the gp120 external surface (SU) envelope protein and a gp41 transmembrane (TM) protein (59,60 and 61). The envelope glycoprotein is responsible for initial interactions between HIV and host cells. This includes binding and entry into host cells, membrane fusion, and syncytium production (58,60,65). The gp120 glycoprotein is divided into distinct domains; those with little variation in amino acid sequences are called constant (C) regions, whereas those with substantial variation are called variable (V) regions (65). The V3 loop, a part of variable region V3, is the major epitome that elicits neutralizing antibody (66,67). Variation in the amino acid sequence of the V3 loop has been associated with viral tropism for specific cell types, such as lymphocytes, monocytes, and central nervous system cells (68,69). In addition, the lipid bilayer is studded with host proteins, including Class I and II major histocompatability complex (MHC) antigens (60).

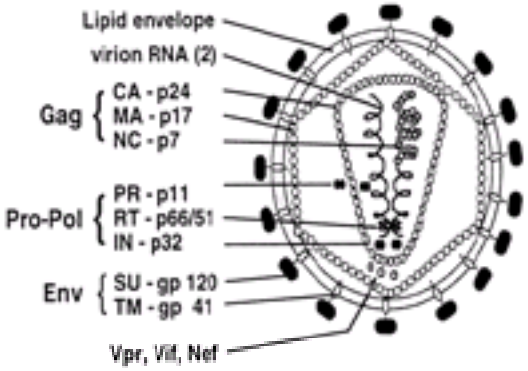


FIGURE 10.11. Human immunodeficiency virus virion structure.

Based on its genetic complexity, HIV is unique among the retroviruses (Fig. 10.12) (57,59,60). In addition to the three structural (essential) genes, *gag, pol,* and *env,* which encode the core proteins, RT enzyme, and envelope proteins, HIV contains an elaborate set of additional (regulatory) genes that determine whether virus is made and, if so, control the level of virus production (59,60,61 and 62,65). These genes function to regulate production of viral proteins. To date, six additional genes have been identified in the HIV genome. As noted in Fig. 10.12, the nine genes are arranged along the viral DNA and flanked by long terminal repeats (LTRs) that do not code for any protein, but rather initiate expression of other viral genes. The identified functions for these genes are listed in Table 10.5. As noted by Geleziunas and Greene (60), it is the distinct but concerted actions of these nine genes that underlie the profound pathogenicity of HIV-1.

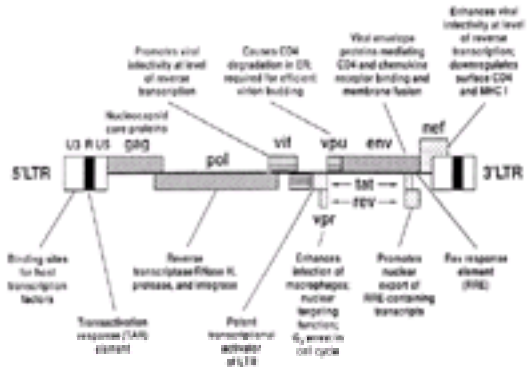


FIGURE 10.12. Genomic structure of HIV-1. The nine known genes of HIV-1 are shown. The 5' and 3' long terminals repeats (LTRs) containing regulatory sequenced recognized by various host transcription factors are depicted. The positions of the Tat and Rev RNA response elements—transactivation response (TAR) element and Rev response element (RRE)—are indicated. From ref. 60, with permission.

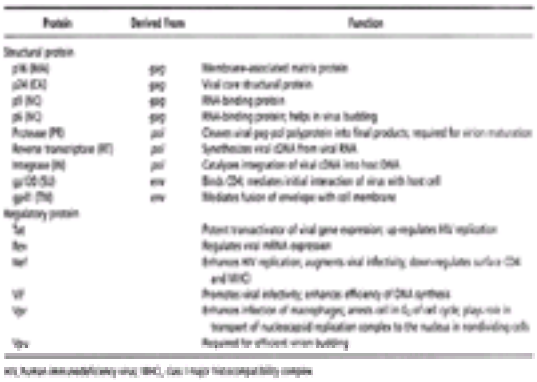


TABLE 10.5. PROTEINS OF HUMAN IMMUNODEFICIENCY VIRUS AND THEIR FUNCTIONS

The *gag*-derived proteins (Fig. 10.12) comprise the structural components of the virus (60,61 and 62,65). These include the p17 matrix (MA) protein as discussed earlier, the p24 core antigen (CA) that forms the structure of the capsid, and the p9 nucleocapsid (NC) protein within the interior of the viral core. In addition, the viral core contains proteins derived from the *pol* gene that are essential for viral replication (60,61 and 62,65). These proteins include RT, which synthesizes viral cDNA from viral RNA; integrase (IN), which catalyzes insertion of viral cDNA into the cellular DNA; and protease (PR), which cleaves the *gag* and *pol* precursor proteins to create the final form of viral structural proteins during virion maturation (60,61 and 62,65).

Several of these regulatory genes accelerate virus replication. The *trans*-activator gene *tat* is a positive feedback regulator that increases its own rate of synthesis and the synthesis of all viral proteins (70). Tat is essential for replication of HIV-1 (60). The *tat* gene is responsible for the greatly increased replication of HIV seen in T_4 cells stimulated by an antigen. The auxiliary proteins Nef and Vif enhance the reverse transcription process (71,72 and 73). Nef is required during the viral production and assembly phase of the HIV life cycle, but its effect is primarily apparent with HIV binding to the target cell and establishment of a provirus (60). The virion infectivity gene *vif* increases the infectivity of the virus particle (60,74,75). As with Nef, Vif is required during viral production and assembly, but its effect occurs during binding and provirus production (60). Vif counteracts an intracellular antiviral activity that inhibits virus replication (76).

Human immunodeficiency virus type 1 contains an unusual genetic switch, the regulator of virion protein expression *rev* (77). The *rev* gene positively regulates expression of virion proteins while it negatively regulates expression of the regulatory genes (60,78,79 and 80). The Rev protein exerts its regulatory activity at the posttranscriptional level by inhibiting viral RNA splicing and activating cytoplasmic transport of the unspliced and single spliced forms of HIV-1 (60,81,82 and 83).

Vpr is a small auxiliary protein found in the preintegration complex that enhances the HIV replication rate in macrophages (60,84). The Vpr protein plays a role during the late stages of virion morphogenesis by promoting the efficient release of budding

virions from the cell surface (85).

Viral Life Cycle

Human immunodeficiency virus type 1 infects mainly $CD4^+$ T lymphocytes and monocytes/macrophages (60,86,87). The CD4 molecule on the surface of these cells serves as the primary receptor for HIV-1 binding to the viral envelope glycoprotein gp120. During primary infection, HIV infects cells of the macrophage lineage (88,89). Dendritic cells interact with mucosal T cells to participate in the initial establishment of infection (90).

Chemokine receptors have been identified as cofactors for viral entry and fusion (91,92,93,94,95 and 96). This finding explains why certain strains of HIV-1 preferentially infected macrophages, while other strains preferentially infected transformed $CD4^+$ T-cell lines (60). Viral tropism for particular cell types is the result of the chemokine receptor used as a cofactor for viral entry (60,91,92,93,94,95 and 96). The CXCR4 chemokine receptor is used by HIV-1 strains displaying transformed T-cell line tropism (96). The CCR5 chemokine receptor is used by macrophage-tropic HIV-1 strains (91,93,95). Human immunodeficiency virus type 1 strains that use CCR5 are termed R5 viruses, and strains using CXCR4 are X4 viruses (97,98). These investigations resulted in the recognition that persons homozygous for a 32-nucleotide deletion in the CCR5 receptor have a high degree of resistance to sexually acquired HIV infection (99,100 and 101). With the heterozygous condition of CCR5, slow progression of HIV disease occurs (99,100). Burger and Weiser (86) also noted that the homozygous deleted CCR5 genotype confers substantial protection from mother-child vertical transmission.

The life cycle of HIV is outlined in Fig. 10.13. The initial step in the life cycle of HIV begins when the virion binds to its future host cell. Following interactions of gp120 with CD4 and one of the chemokine receptors (CCR5 or CXCR4), membrane fusion, which is mediated by gp41, occurs (60). As a result, HIV-1 enters into the host cell. Uncoating occurs, followed by reverse transcription of viral RNA and the production of double-stranded viral DNA (60). HIV-1 integrase then promotes insertion of this viral DNA into the host genome, resulting in HIV-1 provirus. The expression of HIV-1 genes initially is stimulated secondary to the action of host transcription factors with binding sites in the LTR (60). As a result of these enhancer-binding proteins, sequential production of various viral RNAs occurs (60). The first mRNAs produced encode for the Tat, Rev, and Nef regulatory proteins. Tat moves back to the nucleus, where it up-regulates activity of the LTR (60). Rev facilitates production of the viral structural proteins that allow assembly and morphogenesis of virions (60). Influenced by Nef, these HIV-1 virions bud from the host cell. Subsequent infection of other $CD4^+$ cells reinitiates the HIV life cycle (60).

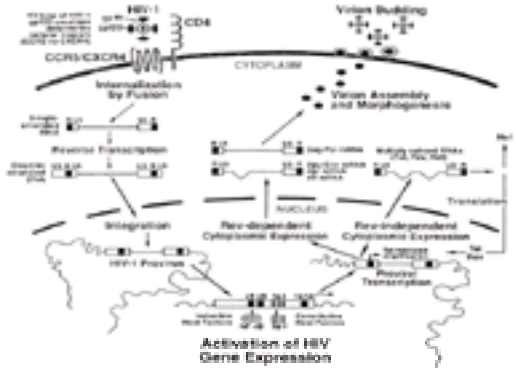


FIGURE 10.13. Life cycle of HIV-1. From ref. 60, with permission.

Disease Progression

Human immunodeficiency virus infection is characterized by substantial viral variability, genotypically, phenotypically, and clinically (61,86,102). Genetically, an infected individual may harbor heterogeneous HIV-1 genomes known as viral quasi-species (61,103). This heterogeneity results from the high level of viral replication that distinguishes HIV from most other human infectious agents (58). The viral replication cycle for HIV is approximately 2 days (104,105). These findings led to the concept that HIV undergoes active and continuous replication, with possibly 300 replication cycles occurring per year and several thousand cycles over the course of infection (104,105). Thus, it is estimated that one billion infectious events take place per day (58,59,104,105). Such a vast number of replication cycles allows the virus ample opportunity to develop genetic diversity (59). This opportunity is enhanced further because viral DNA polymerase is error prone and thus viral replication errors are introduced by the RT enzyme (106,107). An estimated one mismatched nucleotide per genome per round of replication takes place (106,107). In turn, this provides the opportunity for production of a pool of genetic variants, some of which may confer a selective advantage and be retained (102).

Isolates of HIV have phenotypic diversity *in vitro* that correlates with clinical status (86). Species with tropism for T lymphocytes and the ability to induce syncytium formation are associated with advanced disease (108). In contradistinction, phenotypes with tropism for macrophages and that are nonsyncytium inducing are associated with primary and asymptomatic infection (108). Viral phenotypic characteristics also may influence the ability to transmit certain HIV species (86,109). Soto-Ramirez et al. (109) reported that tropism for macrophages is associated with heterosexual transmission.

Great diversity is present in the clinical course and rate of disease progression with HIV infection (60,110). Prior to the availability of highly effective antiretroviral therapies, the average time elapsed from initial infection with HIV to the development of AIDS was 10 to 11 years (111). However, in approximately 20% of HIV-infected individuals, this progression was accelerated and AIDS developed within 5 years (111,112). At the opposite end of the spectrum, an even smaller group (<5%) are long-term nonprogressors (111,112). The group into which these HIV-infected

individuals fall is the result of complex interactions among HIV, host immunogenetic factors (e.g., chemokine receptor status), and the environment (86,113).

Viral replication is influenced by the level of immune activation (114,115). As reviewed by Koenig and Fauci (112), many components of the immune system respond to infection with HIV and are associated with inhibition of viral replication. However, there are circumstances in which specific immune mechanisms actually enhance viral replication (116,117 and 118). Following infection with HIV, the host produces successful protective responses, including generation of envelope-specific antibodies with neutralizing activity, HIV-specific antibodies with neutralizing activity, and HIV-specific cytotoxic T cells to a variety of HIV proteins (112). Current opinion holds that components of the natural or nonantigen-specific immune system (e.g., secretion of cytokines with antiviral activity by activated $CD8^+$ cells) are more important in inhibiting HIV replication (112,119,120).

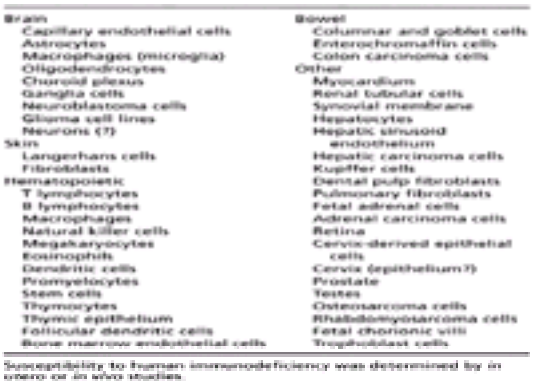
Ambroziak and Levy (58) summarized the characteristics that are common to long-term survivors with HIV infection. The characteristics included (i) low virus load (infected cells and free virus in peripheral blood); (ii) viral isolates from these long-term survivors are relatively noncytopathic; (iii) antibodies to the autologous virus do not enhance infection; and (iv) the $CD8^+$ cell antiviral responses remain strong. A strong antiviral response by $CD8^+$ cells sharply contrasts to the decreased activity seen in HIV-infected individuals progressing to clinical disease (121,122). Importantly, this $CD8^+$ antiviral response suppresses viral replication in $CD4^+$ cells without killing the infected cell (58).

Originally, the consensus belief held that after the initial primary infection with HIV during which high levels of viral replication were present, viral replication entered a long latent phase during which HIV-infected persons were asymptomatic (112). This ultimately was followed by accelerated viral replication and depleted $CD4^+$ T cells, which were thought to precede development of AIDS (112). However, research in the mid-1990s led to the currently held concept that viral replication and turnover of infected T cells are rapid and continuous (104,123,124 and 125). In response, the hematopoietic system replaces the depleted T cells in an attempt by the immune system to limit viral replication (112). Thus, during primary HIV infection, there is a high level of viremia (10^6 to 10^7copies of HIV-1 RNA per milliliter) associated with a precipitous fall in the level of $CD4^+$ T cells, which subsequently is partially restored within weeks as anti–HIV-specific immune responses are induced (112).

Investigators using anti-HIV drugs as probes identified what appeared to be a steady state of HIV in the blood, with billions of virus particles continuously being produced by newly infected cells and then rapidly cleared (104,105). These investigators analyzed plasma levels of HIV RNA as a proxy for the amount of free virus. These studies demonstrated that plasma HIV levels are high and remain so because many new immune cells are constantly being infected. Thus, HIV infection is a dynamic process where there are continuous rounds of *de novo* infection, replication, and turnover. The total CD4 population in peripheral blood in HIV-infected persons doubles every 15 days.

Although the initial studies on HIV focused on its presence in helper T lymphocytes, the virus subsequently has been recovered from macrophages, B lymphocytes, promyelocytes, epidermal Langerhans cells, lymph nodes, bowel epithelium, brain

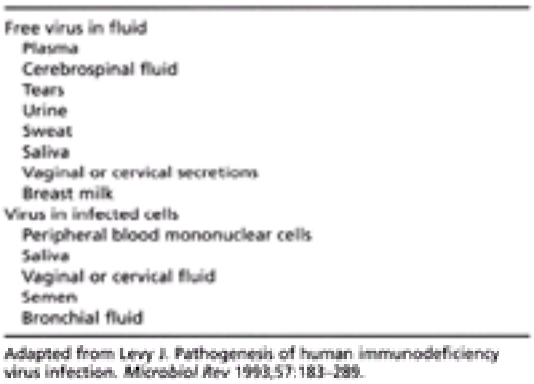
astrocytes, oligodendrocytes, capillary endothelium, and macrophages (56). Table 10.6 lists the human cells that have been shown to be susceptible to HIV. In addition to being detected in these tissues, HIV has been recovered from multiple body fluids (Table 10.7).



Brain	Bowel
Capillary endothelial cells	Columnar and goblet cells
Astrocytes	Enterochromaffin cells
Macrophages (microglia)	Colon carcinoma cells
Oligodendrocytes	Other
Choroid plexus	Myocardium
Ganglia cells	Renal tubular cells
Neuroblastoma cells	Synovial membrane
Glioma cell lines	Hepatocytes
Neurons (?)	Hepatic sinusoid endothelium
Skin	Hepatic carcinoma cells
Langerhans cells	Kupffer cells
Fibroblasts	Dental pulp fibroblasts
Hematopoietic	Pulmonary fibroblasts
T lymphocytes	Fetal adrenal cells
B lymphocytes	Adrenal carcinoma cells
Macrophages	Retina
Natural killer cells	Cervix-derived epithelial cells
Megakaryocytes	Cervix (epithelium?)
Eosinophils	Prostate
Dendritic cells	Testes
Promyelocytes	Osteosarcoma cells
Stem cells	Rhabdomyosarcoma cells
Thymocytes	Fetal chorionic villi
Thymic epithelium	Trophoblast cells
Follicular dendritic cells	
Bone marrow endothelial cells	

Susceptibility to human immunodeficiency was determined by in vitro or in vivo studies.

TABLE 10.6. HUMAN CELLS SUSCEPTIBLE TO HUMAN IMMUNODEFICIENCY VIRUS



Free virus in fluid
Plasma
Cerebrospinal fluid
Tears
Urine
Sweat
Saliva
Vaginal or cervical secretions
Breast milk
Virus in infected cells
Peripheral blood mononuclear cells
Saliva
Vaginal or cervical fluid
Semen
Bronchial fluid

Adapted from Levy J. Pathogenesis of human immunodeficiency virus infection. *Microbiol Rev* 1993;57:183–289.

TABLE 10.7. ISOLATION OF HUMAN IMMUNODEFICIENCY VIRUS FROM BODY FLUIDS

In nearly all HIV-infected patients, HIV-1 RNA can be detected in the plasma after acute infection (126). Early in primary acute infection, there is rapid viral replication that is unopposed by an effective immune response and produces a plasma viremia of 10^6 to 10^7 HIV-1 RNA copies per milliliter (87). There is a concomitant precipitous drop in $CD4^+$ T cells that, within a few weeks, are partially restored as anti–HIV-specific immune responses are elicited (112). The results from the hematopoietic system replacing depleted T cells as the immune system attempts to limit viral replication (112). Following this immune response, the viral load drops dramatically by 2 to 4 log copies per milliliter and reaches a nadir or “setpoint” approximately 3 to 4 months after the onset of symptoms in primary HIV-1 infection

(87). However, even in the face of this reduced viremia, there is continuous viral replication and $CD4^+$ T-cell depletion occurring during all stages of HIV infection (105).

Infectivity

Levy (127) proposed that because of the low level of infectious HIV particles in body fluids, transmission of free virus is less likely than transmission by infected cells. Interestingly, large numbers of HIV-infected cells are present in genital secretions, such as semen and vaginal or cervical fluid (127). Levy stressed the important role of virus-infected cells in the transmission of HIV. He also pointed out that such cells pose a significant problem for antiviral therapy because, in order to eliminate the virus, the HIV-infected cells must be destroyed (127). Such a role of HIV-infected cells may explain the increased risk for HIV transmission seen with genital ulcer disease and its associated inflammatory cell response.

Like all viruses, HIV must enter host cells before it can propagate and/or produce damage. For this to occur, the virus requires a cell surface receptor for attachment and penetration of the host cell (61). For HIV, the CD4 antigen complex is the primary receptor and is present primarily on helper T cells, as well as B lymphocytes, macrophages, lymph nodes, Langerhans cells of the skin, and some brain cells (61). As discussed earlier, secondary HIV-1 receptors (e.g., chemokine receptors) that are required for HIV attachment and fusion have been discovered.

Dendritic cells have emerged as playing an important role in the pathogenesis of HIV infection (112). Dendritic cells are composed of circulating and tissue components (128). The dendritic cells found in the skin and mucosa are known as Langerhans cells (129). Circulating dendritic cells are derived from the bone marrow and traffic within the blood, secondary lymphoid organs, and skin (128,130,131). The primary function of these dendritic cells is to capture, process, and present antigens to T cells (112). t mucosal sties (and skin), primary HIV infection includes the capture of virions by and/or infection of dendritic cells contained in the epithelium and subsequent migration of infected dendritic cells to regional draining lymph nodes (132). These lymph nodes are the sites where HIV infection becomes established (132).

Three principal means of HIV transmission have been demonstrated (58,127,133). HIV may be transmitted by blood or blood products, sexual contact (homosexual or heterosexual), and perinatally (mother to child). Initially, early in the AIDS epidemic, HIV transmission was attributed to sexual contact, transfusion with infected blood, and intravenous drug use (134). Subsequently, mother-child transmission was recognized and, as a result, *in utero* (transplacental), intrapartum, and breast-feeding were recognized as routes of HIV infection (58,135,136 and 137). As noted by Ambroziak and Levy (58), transmission of HIV correlates with high levels of infectious virus in these body fluids and the nature and duration of contact with infected fluids. With introduction of molecular techniques (e.g., polymerase chain reaction [PCR]), quantitation of virus in the blood demonstrated an association between viral load, $CD4^+$ cell count, and disease stage (138). HIV viral load is highest during the initial acute infection, drops dramatically during the asymptomatic stage, and rises again as HIV infection progresses to AIDS (58). In HIV-infected but healthy individuals, one in 1,000 to 10,000 peripheral blood mononuclear cells (PBMCs) are infected with HIV (139,140). On the other hand, in AIDS patients, approximately one in ten PBMCs is infected (141). Based on an estimated five

million PBMCs per milliliter, healthy HIV-infected persons have approximately 5,000 infected PBMCs per milliliter and 100 infectious HIV particles per milliliter (58). Levy (140) has suggested that HIV-infected cells constitute the major source of infectious virus in the blood.

Transfusion of blood from an HIV-infected donor is a very efficient means of transmission. The risk is dependent on disease stage, viral load, and phenotype of the predominant HIV strain in the donor (140). Prior to the recognition that HIV was present in blood and blood products, thousands of transfusion recipients and hemophiliacs were infected with HIV (58). Improved donor screening techniques by blood banks and treatment of blood products has virtually eliminated receipt of blood and/or blood products as a risk for HIV transmission (58).

Among IDUs, shared needles are the responsible risk factor. The risk for HIV transmission among IDUs correlates directly with the incidence of needle sharing and the viral load of HIV in IDUs (142). The importance of viral load as a risk factor for parenteral transmission of HIV is demonstrated by the fortunate fact that transmission via accidental needle sticks is not a major cause of infection; most needle sticks do not transfer appreciable amounts of blood (58). This is in contradistinction to hepatitis B virus infection, where 100 million to one billion viral particles per milliliter of blood are present and the risk of needle-stick transmission is substantially increased (143).

For transmission of HIV through sexual contact, the presence of virus in genital fluids is a key factor (58). Both seminal and vaginal cells can contain virus as well. It has been suggested that, similar to parenteral transmission, infected cells are the major source of HIV (58). Consequently, an increased risk of sexual transmission has been seen with advanced disease in infective male partners (144,145). Multiple investigations have demonstrated that the presence of other STDs, ulcerative (syphilis, genital herpes, chancroid) and nonulcerative (gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis [BV]), is associated with an increased risk for HIV transmission (146,147,148,149,150 and 151).

Prior to the introduction of antiretroviral therapy in the management of HIV-infected pregnant women, mother-infant transmission rates ranged from 13% to 40% (152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173 and 174). The majority of the cases of mother-child transmission occurs during the intrapartum period (175,176 and 177). In utero or antepartum transmission while less common, is also well documented (175,176 and 177). Breast-feeding in the postnatal period also has been shown to be a source for mother-child transmission of HIV (177,178,179,180,181,182,183,184,185,186,187,188,189 and 190). Viral load of HIV has been demonstrated to be a critically important determinant of mother-child (vertical) transmission of HIV (191,192 and 193). Thus, acute HIV infection with its high level of viral load is a high-risk situation for transmission of HIV during the intrapartum period or while breast-feeding (58). Similarly, advanced HIV disease, which also is associated with high-level viremia, carries a high risk for perinatal transmission (194).

Clinical Features Of HIV Infection

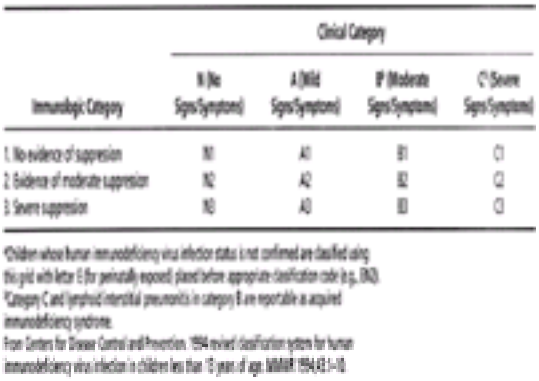
Infection with HIV produces a wide spectrum of disease. Although AIDS is the lethal end stage of this spectrum, it is only the “tip of the iceberg” and represents the

minority of HIV-infected individuals. In 1982, the CDC issued a surveillance case definition based on the occurrence of malignancy (e.g., Kaposi sarcoma) or an infection (e.g., *Pneumocystis carinii* pneumonia [PCP]) that was moderately to highly predictive of a defect in cell-mediated immunity in the absence of previously recognized predisposing conditions or causes of cell-mediated immune deficiency (195). At that time, evidence for infection with HIV was not required. In 1985, the CDC expanded the list of opportunistic infections indicative of AIDS and included evidence of infection with HIV (i.e., antibody, antigen, or culture) in the case definition for AIDS (196). In 1987, the CDC again redefined the criteria for the diagnosis of AIDS (197). A case of AIDS was defined as an illness characterized by the presence of one or more "indicator" diseases, depending on the status of laboratory evidence of HIV infection.

The most recent revision of these criteria occurred in 1993, when the CDC expanded the surveillance case definition of AIDS to include all persons with a $CD4^+$ T-lymphocyte count less than 200 per mL or whose $CD4^+$ T-lymphocyte percentage is less than 14% (Table 10.8) (198). In addition, three conditions were added to the list of AIDS-defining illnesses (clinical category C): invasive cervical cancer, recurrent pneumonia, and pulmonary tuberculosis. Of interest to clinicians providing health care for women were several conditions listed in category B: (i) vulvovaginal candidiasis, which is persistent, frequent, or poorly responsive to therapy; (ii) cervical dysplasia (moderate or severe) or carcinoma *in situ;* and (iii) pelvic inflammatory disease (PID), particularly if complicated by tuboovarian abscesses. The 1993 revision had a much greater impact on reporting than the previous revisions of the AIDS surveillance definition in 1985 and 1987 (199). During the first 3 months of 1993, there was a threefold increase in cases of AIDS reported to the CDC, of which 60% met only the new criteria. Persons with immune suppression comprised the largest component of the increase (89%); only 9% had pulmonary tuberculosis, 1% had recurrent pneumonia, and less than 1% had invasive cervical cancer (200). Carpenter et al. (201) reported that the most common AIDS-defining illnesses in women include PCP; *Candida* esophagitis; cryptococcal meningitis; wasting syndrome, herpes simplex virus (HSV) bronchitis, pneumonia, esophagitis, or ulcers of longer than 1-month duration; cytomegalovirus (CMV) disease; tuberculosis; central nervous system toxoplasmosis; and lymphoma.

TABLE 10.8. 1993 REVISED CLASSIFICATION SYSTEM FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND EXPANDED SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS

Because the clinical characteristics of AIDS in children are different from those in adults, the CDC definition of AIDS for children less than 13 years of age proposed in 1987 differed from that of adults (202). Because of passively acquired maternal antibodies, the laboratory criteria for HIV infection in children less than 15 months of age are more stringent. In children, clinical AIDS is characterized by multiple or recurrent serious bacterial infections and lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia. In September 1994, the CDC proposed a revised classification system for HIV infection in children less than 13 years of age (203). The new system classifies infected children into mutually exclusive categories according to three parameters: (i) infection status, (ii) clinical status, and (iii) immunologic status (Table 10.9). The criteria for diagnosis of HIV infection in children are shown in Table 10.10. For specific information on the age-based immunologic categories and clinical categories for children with HIV infection, the reader is referred to the CDC's 1994 revised classification system (203).



	Clinical Category			
Immunologic Category	N (No Signs/Symptoms)	A (Mild Signs/Symptoms)	B (Moderate Signs/Symptoms)	C[1] (Severe Signs/Symptoms)
1. No evidence of suppression	N1	A1	B1	C1
2. Evidence of moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

[1]Children whose human immunodeficiency virus infection status is not confirmed are classified using this grid with letter E (for perinatally exposed) placed before appropriate classification code (e.g., EN2).
[2]Category C and lymphoid interstitial pneumonitis in category B are reportable as acquired immunodeficiency syndrome.
From Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43:1–10.

TABLE 10.9. 1994 CENTERS FOR DISEASE CONTROL AND PREVENTION REVISED CLASSIFICATION[a] FOR PEDIATRIC HUMAN IMMUNODEFICIENCY VIRUS

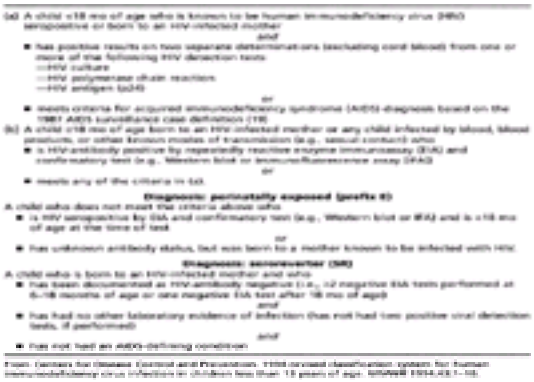


TABLE 10.10. DIAGNOSIS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

IN CHILDREN

Pathogenesis of HIV Infection

The pathogenesis of HIV infection has been reviewed extensively by several authors (57,58,60,61 and 62,87,110,111,140,204,205). Figure 10.14 shows the steps involved in the pathogenesis of HIV infection (205). The pathogenesis of HIV is summarized briefly here. The initial step is entry of the virus into an individual primarily by infecting activated T cells, resident macrophages, or dendritic cells in the mucosal of the bowel or genital tract. With sexual transmission, the initial cellular targets of HIV are tissue dendritic cells (Langerhans cells), which are located in the lamina propria below the epithelium (206). Transmitted HIV usually is macrophage-tropic and lacks an ability *(in vitro)* to induce syncytial formation (89,207). The envelope protein Gp120 binds to the CD4 molecule on dendritic cells, but viral entry into the cell requires the presence of a coreceptor, which in the case of macrophage-tropic strains of HIV is CCR5, a surface chemokine receptor (91,95,96). These viruses requiring CCR5 as a coreceptor have been named R5 viruses (208). Thus, dendritic cells, which express the viral coreceptors CD4 and CCR5, are selectively infected by R5 (macrophage-tropic) strains (208). Within 2 days infection, these cells fuse with $CD4^+$ T-cell lymphocytes and spread to draining lymph nodes, from whence systemic dissemination occurs and HIV-1 can be cultured in plasma from 4 to 11 days after infection (209). The risk of acquiring HIV via sexual transmission is increased in the presence of breaks in the mucosal barrier and increased inflammation associated with genital ulcer disease, urethritis, or cervicitis (210).

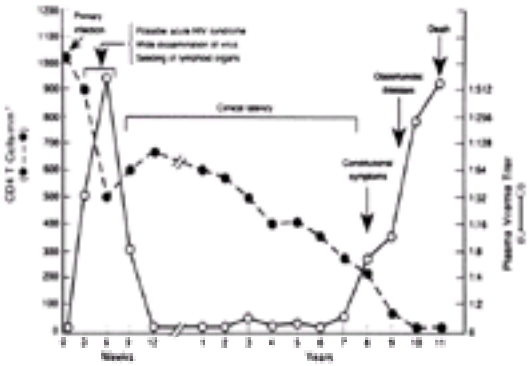


FIGURE 10.14. Relationship among peripheral blood $CD4^+$ T-cell count, plasma viremia, and clinical disease progression. (From Pantaleo G, Graziosi C, Fauci AS. The immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med* 1993;328:327–335, with permission.)

In the case of parenteral transmission, HIV initially may target circulating dendritic cells (macrophage-tropic, R5) or $CD4^+$ T-cell lymphocytes. T-cell–tropic HIV requires

the coreceptor CXCR4, another surface chemokine receptor, for cell entry to occur (208). Once cell entry occurs, the same process of pathogenesis ensues. With perinatal transmission, both mechanisms may play a role.

There occurs a rapid rise in plasma levels of HIV after infection, and widespread dissemination of HIV occurs in association with seeding of lymphoid organs (211,212 and 213) and trapping by follicular (circulating) dendritic cells (214). Following the initial rise in plasma HIV level (>1 million HIV-1 RNA particles per milliliter), there is a marked reduction in plasma viremia to a steady-state level of viral replication (setpoint) (138,215,216,217,218 and 219). This decrease in plasma viremia is the result of virus-specific immune responses that limit viral replication; HIV-1–specific cytotoxic T lymphocytes appear concomitant with declining titers of HIV (219,220).

A viral setpoint, which varies for each individual, is established following this initial drop in HIV viral load (206). Several factors that determine the setpoint of viral load have been proposed, including (i) genetic differences in coreceptors (100,221); (ii) qualitative differences in the immune response (222,223,224 and 225); and (iii) differences in the virulence of HIV strains (226,227). Lower levels of viremia (setpoint) are associated with slower disease progression and a better prognosis (58,60,86,87,228).

The pathogenesis of HIV infection progresses through three stages: (i) initial acute infection (early stage); (ii) clinically asymptomatic stage; and (iii) symptomatic stage (severe infection, AIDS) (58). These stages will be described fully in the subsequent sections.

Following the significant decline in viremia at the end of the acute infection stage, HIV-infected persons enter the asymptomatic stage (persistent or latent state) in which virus replication persists, particularly in lymph nodes and PBMCs, with low measured levels in the blood. The mechanism by which HIV causes a loss of immune response has been one of the major mysteries of AIDS (61). Reports by Wei et al. (104) and Ho et al. (105) demonstrating both high levels of viral production and concomitant rapid production of $CD4^+$ T cells suggest that continuous rapid virus production and $CD4^+$ cell depletion occur at all stages of infection. As $CD4^+$ cell counts fall below 300 cells/mL and high levels of HIV again appear in the blood, individuals begin to become symptomatic. At this time, a reduction in ant-viral $CD8^+$ cell responses also occurs. As the immune system deteriorates, the opportunistic infections and malignancies that define a diagnosis of AIDS ultimately appear.

Levy (61) noted that as individuals become symptomatic and develop AIDS, HIV has characteristics distinct from the virus recovered soon after initial infection. Characteristically, the virus assumes properties associated with virulence in the host (Table 10.11). These characteristics include an enhanced cellular host range, rapid kinetics of replication, $CD4^+$ cell cytopathicity, resistance to neutralization, and sensitivity to enhancing antibodies. Studies by Levy suggest that loss of $CD8^+$ cell activity is a major factor in diseases progression and allows emergence of these cytopathic viral strains, which then lead to a loss of $CD4^+$ cells. The factors contributing to HIV-induced immune deficiency are listed in Table 10.12.

Enhanced cellular host range
Rapid kinetics of replication
High titers of virus production
Disruption or alteration of cell membrane permeability
Increased syncytium induction
Efficient cell killing
No latent state *in vitro*
Lack of sensitivity to suppression
Sensitivity to antibody-mediated enhancement of infection

From Levy J. Pathogenesis of human immunodeficiency virus infection. *Microbiol Rev* 1993;57:183–289, with permission.

TABLE 10.11. CHARACTERISTICS OF HUMAN IMMUNODEFICIENCY VIRUS STRAINS ASSOCIATED WITH VIRULENCE IN THE HOST

Direct cytopathic effects of HIV and its proteins on $CD4^+$ cells: cell destruction; effect on stem cells; effect on cytokine production; effect on electrical potential of cells; enhanced fragility of $CD4^+$ cells
Effect of HIV on signal transduction and cell function: induction of apoptosis
Cell destruction via circulating envelope gp120 attachment to normal $CD4^+$ cells: ADCC, CTL
Immunosuppressive effects of immune complexes and viral proteins (e.g., gp120, gp41, Tat)
Anti-$CD4^+$ cell cytotoxic activity ($CD8^+$ and $CD4^+$ cells)
$CD8^+$ cell suppressor factors
Anti-$CD4^+$ cell antibodies
Cytokine destruction of $CD4^+$ cells

From Levy J. Pathogenesis of human immunodeficiency virus infection. *Microbiol Rev* 1993;56:183–289, with permission.
ADCC, antibody dependent cellular cytotoxicity; CTL, cytotoxic T-lymphocytes.

TABLE 10.12. FACTORS INVOLVED IN HUMAN IMMUNODEFICIENCY VIRUS-INDUCED IMMUNE DEFICIENCY

As reviewed by Levy (229), the pathogenesis of HIV progresses through three stages. In the initial acute infection (early stage), $CD4^+$ T cells and macrophages are infected with HIV. Viral replications result in high levels of viral load in plasma reaching 5,000 particles per milliliter. During this early stage, prior to production of an immune response, lymphoid tissue and many other cells are infected. Embretson et al. (230) demonstrated that as many as 250 billion cells could be infected during this early stage of HIV infection. Initially, $CD4^+$ T cells decrease and $CD8^+$ cells increase in number, but return to baseline once the cellular and humoral immune responses to HIV occur. Similarly, as a result of the immune response, viral levels also decline dramatically. However, a small number of infected cells continue to replicate HIV.

The second (asymptomatic) stage of HIV infection commences several months after the primary acute infection and ranges in duration from as short as 1 year to over a decade (58). During the asymptomatic stage, detectable, often high, levels of HIV replication occur (231); thus, the initial concept that viral infection was latent during this stage is no longer accepted. Rather, studies using quantitative PCR technology

to measure the level of HIV-1 RNA in plasma revealed a steady-state model with rapid production and turnover of HIV in which infection, cell death, and replacement are all in equilibrium (104,105,232). $CD8^+$ cell antiviral activities control the virus somewhat during this stage (58). The length of the asymptomatic stage probably is determined by the host cellular immune response (233). During the asymptomatic stage, $CD4^+$ T cells begin a slow progressive decline. A concomitant increase in viral load is associated with progression to the final (symptomatic) stage (58,229). $CD8^+$ cell function depends on adequate amounts of interleukin-2 (IL-2), which is produced by $CD4^+$ T cells (58). The decline in $CD4^+$ T cells over time may, therefore, be responsible for the reduction in $CD8^+$ cell antiviral immune responses (234). As a result of declining $CD8^+$ cell activity, increased replication of a pathogenic HIV isolate leads to the final reduction in $CD4^+$ T-cell numbers heralding the onset of symptomatic HIV infection (AIDS) (232).

Viral Load and Pathogenesis

The introduction of quantitative methods for measurement of persons infected with HIV-1 (235,236) and the subsequent development of quantitative competitive PCR, which can measure HIV-1 RNA levels in plasma during clinically asymptomatic and symptomatic stages (231), were major contributors to understanding the pathogenesis of HIV infection. As noted earlier, this resulted in a new paradigm that detectable, often high, levels of HIV-1 replication occurred during asymptomatic as well as symptomatic stages of HIV infection (231).

Over the past decade, numerous investigations have documented the critical role that viral load plays in the pathogenesis of HIV infection and in determining clinical outcome as well as response to antiretroviral therapy (101,231,235,236,237,238,239,240 and 241). Figure 10.15 shows the relationship among viral load, $CD4^+$ T-cell count, and clinical symptoms. The importance of viral load applies to tissue and HIV-infected PBMCs as well as plasma (212,213,242,243).

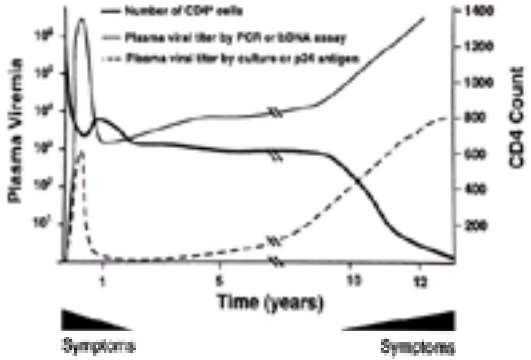


FIGURE 10.15. Role of viral load in the natural history of HIV-1 infection. From Grant RM, Saag MS. Laboratory testing for HIV-1. In: Sonde MA, Volberging PA. The medical management of AIDS. Philadelphia: WB Saunders, 1999;43–65, with permission.

Mellors et al. (244) reported that in the Multicenter AIDS Cohort Study that plasma HIV-1 RNA level measured after seroconversion was a better predictor of progression to AIDS in homosexual and bisexual men than the $CD4^+$ T-cell number. Subsequently, Fang and colleagues (245) demonstrated that the relationship of viral load with disease progression was similar in men and women.

Once HIV antibody testing became available, an acute clinical HIV infection was recognized. Cooper and coworkers (246) first reported this clinical illness associated with primary HIV infection in 11 of 12 homosexual men with documented seroconversion. These men presented with a “mononucleosis like” illness with fevers, sweats, lethargy, malaise, myalgias, arthralgias, headaches, diarrhea, sore throat, lymphadenopathy, and a maculopapular rash on the trunk. The illness was characterized by sudden onset with duration of 3 to 14 days. Neurologic manifestations, such as meningoencephalitis, myelopathy, peripheral neuropathy, and Guillain-Barré syndrome, also were seen with primary HIV infection (246). In addition, abnormal liver function test results have been reported in association with primary HIV infection. As noted by Abrams (247), this earliest clinical syndrome of HIV infection probably was frequently seen but not recognized as a unique disease entity early in the AIDS epidemic. The clinical manifestations of primary HIV-1 infection are listed in Table 10.13. The reported incubation time for acute primary HIV infection has ranged from 3 days to 3 months, with a 3-to 6-week period most commonly seen (Fig. 10.16) (87,205,206,246).

General/ Constitutional	Dermatologic	Gastrointestinal	Pulmonary	Neurologic
Fever	Maculopapular rash	Oral/oropharyngeal/ esophageal candidiasis	Cough	Headache, retroorbital pain, photophobia
Pharyngitis (nonsuppurative)	Roseola-like rash	Nausea/vomiting		Cognitive/affective impairment
Lymphadenopathy	Vesiculopustular rash	Anorexia		Peripheral neuropathy
Arthralgia	Diffuse urticaria	Abdominal pain		Myelopathy
Myalgia	Desquamation of palms or soles	Diarrhea		Radiculopathy
Fatigue/malaise	Mucocutaneous ulceration			Brachial neuritis
Weight loss	Alopecia			Guillain-Barré syndrome

From Vergis EN, Mellows BR. Natural history of HIV-1 infection. Infect Dis Clin North Am 2000;14:809–825, with permission.

TABLE 10.13. CLINICAL SYMPTOMS AND SIGNS OF ACUTE HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 INFECTION

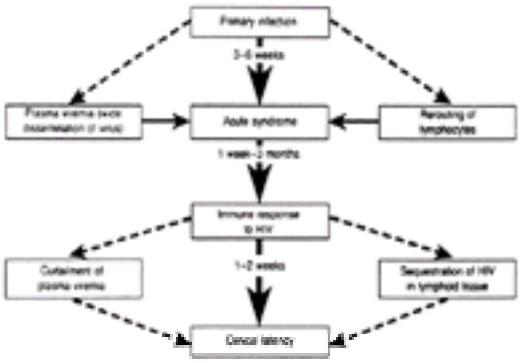


FIGURE 10.16. Early stages of human immunodeficiency virus disease progression. (From Pantaleo G, Graziosi C, Fauci AS. The immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med* 1993;328:327–335, with permission.)

The most common signs and symptoms of acute HIV-1 include fever, fatigue, rash (usually maculopapular), headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, aseptic meningitis, weight loss, gastrointestinal distress (nausea, vomiting, or diarrhea), night sweats, and oral or genital ulcers (87,206,247,248). The duration of acute HIV infection usually is less than 14 days, but acute illness may last up to 10 weeks or more (206,249). As noted by Kahn and Walker (206), the severity and duration of acute HIV infection has prognostic implications, with severe and prolonged symptoms associated with rapid progression of HIV disease (250,251). Schacker et al. (249) prospectively followed a cohort of individuals at risk of HIV infection and reported that among those persons who became infected, 7% had acute symptomatic infection.

The symptoms and signs of acute HIV infection are nonspecific; thus, diagnosis of the acute illness often poses a challenge for health care providers (206). An important aspect is obtaining an accurate history of exposure (206). Therefore, a diagnostic workup for acute HIV infection is indicated in patients with signs and symptoms consistent with such a diagnosis and a history of exposure to a person with known or possible HIV infection (206). Differentiation from infectious mononucleosis (Epstein-Barr virus) infection is the most common concern. Kahn and Walker (206) noted that some symptoms are very suggestive of acute HIV infection in cases where a history of exposure is present. These symptoms include a maculopapular rash involving the trunk (40% to 80% of persons with acute HIV infection), acute meningoencephalitis syndrome, and mucocutaneous ulceration involving the oral cavity or genital area. Another helpful differential finding is the acute onset of primary HIV infection.

Laboratory studies obtained during acute HIV infection may demonstrate lymphopenia and thrombocytopenia (206). Atypical lymphocytes are an infrequent finding. Initially there is a decrease in $CD4^+$ T-cell numbers, followed by lymphocytosis (predominantly $CD8^+$ cells) resulting in inversion of the ratio of $CD4^+$ cells to $CD8^+$ cells (87). Individuals with primary acute HIV infection fall into category A of the 1993 CDC classification scheme for HIV infection.

The enzyme-linked immunoabsorbent assays (ELISAs) commonly used to diagnose established HIV-1 infection first become positive 22 to 27 days after acute infection (252). They usually are negative in patients who present with acute HIV infection, and the tests cannot be relied on to make a diagnosis of acute HIV infection (206). Home tests commercially available also measure antibody and cannot be relied on to diagnose acute infection. Both p24 antigen (serum or plasma) and high plasmal viral RNA levels have been used to diagnose cases of acute HIV (215,216). Detection of high-titer viral RNA or viral p24 antigen in a patient with a negative test for HIV-1 antibodies establishes the diagnosis of acute HIV infection (206,216,253). Of these two available tests, viral RNA has greater sensitivity. Viral RNA assay detects HIV infection 3 to 5 days earlier than p24 antigen tests (252,254) and 1 to 3 weeks earlier than standard serologic tests (255). Kahn and Walker (206) claim that in their experience (AIDS Programs in San Francisco and Boston), the levels of viral RNA are always greater than 50,000 molecules per milliliter in patients with symptomatic acute HIV infection.

Once the diagnosis of acute HIV infection has been confirmed, early treatment with maximally suppressive combination antiretroviral therapy should be considered (206,256). This recommendation is based on several pieces of evidence, including (i) initial viral isolates represent a fairly homogenous swarm of viruses (89,207) that may be susceptible to combination therapy (206); (ii) early intervention restores virus-specific cellular immune responses that control viremia (216); and (iii) early intervention may limit the extent of viral dissemination, restrict damage to the immune system, and reduce the possibility of disease progression (206). In response to this evidence, a panel of experts from the International AIDS Society-USA recommended that immediate therapy be considered for persons with acute HIV infection (256).

Asymptomatic HIV Infection

Following resolution of the symptoms of primary HIV-1 infection and the appearance of an antiviral immune response, patients enter an asymptomatic (or minimally symptomatic) state that typically lasts 7 to 11 years (can be as short as 1 year or as long as nearly 2 decades) before development of overt immunodeficiency. Asymptomatic HIV-seropositive individuals currently constitute the largest group of HIV-infected persons; the majority of HIV-infected individuals are entirely asymptomatic. However, these asymptomatic HIV-seropositive persons are at risk for development of symptomatic disease over time. It is generally believed that over an approximately 10-year period, in the absence of antiretroviral therapy, nearly all HIV-infected individuals will progress to symptomatic disease (56,57,61,87,111,140,204,205,229,233).

During the asymptomatic stage of HIV infection, $CD4^+$ T cells slowly begin to decline in number (58). As discussed previously, viral replication is somewhat controlled by $CD8^+$ cell antiviral activities (58). However, HIV infection progresses over time. This progression is characterized by gradual decline of $CD4^+$ T cells (approximately 50 to 75 cells per year) and increasing viremia as severe symptomatic HIV infection (AIDS) commences (257).

As noted by Vergis and Mellors (87), the absolute $CD4^+$ T-cell count can be used as

an indicator of immunologic disease progression. Thus, based on $CD4^+$ cell counts, HIV disease is categorized as early ($CD4^+$ >500 cells/mL), mid (200 to 500 cells/mL), advanced (50 to 200 cells/mL), or end stage (<50 cells/mL). With $CD4^+$ counts greater than 500 cells/mL, patients usually remain asymptomatic with the exception of mild or moderate lymphadenopathy (formerly persistent generalized lymphadenopathy). If symptoms occur, they are primarily dermatologic in nature (87). Similarly, most patients with $CD4^+$ counts in the200 to 500 cells/mL range are symptomatic or have mild disease.

Symptomatic HIV Infection

Ultimately, in most HIV-infected persons, the reduction in $CD4^+$ T-cell level and the concomitant increased viral load result in progression of HIV disease to the symptomatic stage (58). With $CD4^+$ counts in the 200 to 500 cells/mL range, some individuals will develop mild symptomatic disease (87). Mild disease is characterized by worsening of chronic skin conditions, recurrent herpes simplex disease, varicella-zoster virus disease, oropharyngeal or vaginal candidiasis, oral hairy leukoplakia, recurrent diarrhea, intermittent fever, or unexplained weight loss (87). Bacterial infections, such as sinusitis, bronchitis, or pneumonia, are common. In addition, myalgias, arthralgias, headache, and fatigue are commonly noted.

When $CD4^+$ cell counts fall into the 50 to 200 /mL range, patients have advanced immunodeficiency and are classified as having AIDS according to the current 1993 CDC definition (87). In this advanced stage, opportunistic infections such as PCP, *Toxoplasmosis* encephalitis, cryptosporidiosis, isoporosis, tuberculosis, and esophageal candidiasis are frequent occurrences. The symptoms worsen in patients who developed symptoms during previous stages (87). Neurologic complications include neuritis, myelitis, cranial nerve palsies, and peripheral neuropathy (258). Human immunodeficiency virus retinopathy with cotton-wool spots may occur. In women, invasive cervical carcinoma may occur (259). Idiopathic thrombocytopenia, anemia, and neutropenia also occur (260).

As $CD4^+$ cell levels fall below 50 cells/mL, patients either enter end-stage immunodeficiency. Diseases more likely to occur with end-stage disease include disseminated *Mycobacterium avium* complex (MAC) disease, cryptococcal meningitis, progressive multifocal leukoencephalopathy, invasive aspergillosis, disseminated coccidioidomycosis, disseminated histoplasmosis, and invasive *Penicillium marneffei* disease (87). Progressive wasting also occurs during end-stage disease.

The 1993 CDC revised classification system for HIV infection (Table 10.8) places in clinical category B symptomatic conditions occurring in an HIV-infected person that are either (i) attributed to HIV infection or are indicative of a defect in cell-mediated immune response or (ii) considered to have a clinical course or to require management that is complicated by HIV infection and are not included as an AIDS indicator condition. Of note in women are (i) vulvovaginal candidiasis, which is persistent, frequent, or poorly responsive to treatment; (ii) cervical dysplasia (moderate to severe) and carcinoma *in situ;* and (iii) PID, especially if complicated by tuboovarian abscesses.

Clinical category C includes the 25 AIDS indicator conditions (Table 10.8). With the

1993 revision, invasive cervical cancer, pulmonary tuberculosis, and recurrent pneumonia were added to the list of AIDS indicator conditions. Persons with constitutional symptoms consistent with the former definition of severe AIDS-related complex are included in category A. These patients present with unexplained fevers, significant weight loss, and/or diarrhea. The patients with progressive wasting syndrome may die without ever developing a diagnosed AIDS opportunistic infection or malignancy. Persons infected with HIV who have significant neurologic disease (without opportunistic infection or malignancy diagnostic of AIDS) are placed in either category B (peripheral neuropathy) or category C (encephalopathy). Infection with HIV is complicated by a variety of central nervous system disorders that are common and produce significant morbidity (261,262 and 263). Not only do the neurologic complications result from opportunistic infections and neoplasms, but they also result from direct nervous system infection by HIV (264). The neurologic complications of HIV infection generally fall into one of three categories: (i) AIDS dementia syndrome, (ii) myelopathies, or (iii) peripheral neuropathies.

Patients with AIDS fall into clinical categories C (C1–C3), B3, and A3. The latter two categories are based on $CD4^+$ cell counts less than 200 m/L or less than 14% $CD4^+$ cells. Although these classification schemes provide a more precise definition and more accurate extent of HIV infection, the groupings are somewhat artificial in that HIV infection is a continuum that progresses from the acute syndrome through an asymptomatic stage, to ultimate clinical disease and death.

Determinants of HIV Disease Progression

As reviewed by Tsoukas and Bernard (265), many clinical and laboratory markers have been used to determine the prognosis of HIV infection. However, recent investigations have demonstrated that the level of plasma HIV-1 RNA (i.e., viral load) is the single best predictor of the risk of HIV disease progression to AIDS and death due to AIDS (238,244,257,266,267 and 268). For example, Mellors et al. (267) noted in a cohort of homosexual men with HIV-1 RNA levels (branched DNA signal amplification) greater than 30,000 copies/mL that 80% developed AIDS within 6 years, whereas in patients whose HIV-1 RNA levels were £500 copies/mL only 5.4% developed AIDS within 6 years. The branched DNA signal amplification assay gives HIV-1 RNA levels approximately one half of those seen with RT-PCR (87). O'Brien and coworkers (268) showed similar findings in a group of HIV-infected hemophiliacs. These authors noted that 10 years after seroconversion, progression to AIDS occurred in 72%, 52%, 22%, and 0% among individuals with plasma HIV-1 RNA levels determined by RT-PCR of ³100,000, 10,000 to 99,999, 1,000 to 9,999, and less than 1,000 copies/mL, respectively.

Thus, studies in both recent seroconverters and chronically infected persons have documented that plasma HIV-1 RNA level is a better predictor of progression to AIDS than previously used predictor markers such as $CD4^+$ T-cell count, b_2-microglobulin, neopterin, or clinical symptoms (87). However, as demonstrated by Mellors et al. (267), although $CD4^+$ cell counts are not as reliable a predictor of progression as HIV-1 RNA levels, $CD4^+$ cell counts do provide additional prognostic information. Thus, it is recommended that both plasma HIV-1 RNA levels and $CD4^+$ cell counts be used to determine the risk of disease progression and response to antiretroviral therapy (87).

Diagnosis Of HIV Infection

As described earlier, HIV infection encompasses a broad spectrum of disease, ranging from asymptomatic seropositivity to full-blown AIDS. It is characterized by a predictable, progressive derangement of immune function of which AIDS is a late manifestation. Establishment of a diagnosis of HIV infection before the development of symptomatic HIV disease or AIDS is important for several reasons. It allows patients to receive optimal medical care as early as possible in the disease, with the resultant opportunity to prevent complications (i.e., prophylaxis against PCP). Second, there is the potential to use antiretroviral therapy in the early stages of HIV infection to delay progression to AIDS (if such an approach is shown to work). Third, diagnosis of asymptomatic HIV-infected individuals allows the opportunity to prevent transmission of HIV. Fourth, in pregnant women, treatment with antiretroviral drugs may prevent vertical transmission of HIV and prevent adverse effects of opportunistic infections in the mother or fetus/newborn.

Both AIDS and the group of symptomatic diseases designated as category B are clinical diagnoses that may be substantiated by evidence of HIV infection. As discussed in the previous section on clinical presentation, in 1986 and 1987 the CDC revised the surveillance definition for AIDS to allow utilization of laboratory evidence for HIV infection and developed a classification system for HIV infection (197,269). In 1993, the CDC further revised the classifications (Table 10.8) to include immunologic parameters. Only those conditions in categories A1, B1, and C1 to C3 fulfill the CDC requirements for reportable diagnosis of AIDS. The conditions in category B are indicative of immune suppression or are influenced by HIV infection.

Persistent generalized lymphadenopathy is diagnosed by the presence of lymphadenopathy in at least two extrainguinal lymph node groups and a biopsy that reveals reactive hyperplasia in the B-cell region of the lymph node.

Because only about half of symptomatic HIV-infected children fulfilled the criteria of the CDC surveillance definition for AIDS, the CDC developed a separate classification system for HIV infection in children under 13 years of age (202,270). In 1994, the CDC revised the classification system for HIV infection in children less than 13 years of age (203). The CDC definition of HIV infection in children is summarized in Table 10.10. The immunologic categories and clinical categories for children with HIV infection are given in Table 10.14 and Table 10.15, respectively.

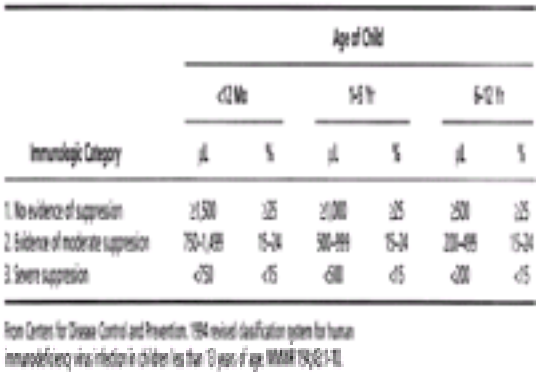


TABLE 10.14. IMMUNOLOGIC CATEGORIES BASED ON AGE-SPECIFIC CD4+ T-LYMPHOCYTE COUNTS AND PERCENTAGE OF TOTAL LYMPHOCYTES

TABLE 10.15. CLINICAL CATEGORIES FOR CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The majority of HIV-infected adults fall into the asymptomatic infection group of category A. In these individuals, the diagnosis of HIV infection requires laboratory evidence that the virus is present. Diagnostic tests for HIV include antibody testing, antigen detection, viral culture, nucleic acid amplification test, and PCR.

Confirmatory Laboratory Tests

Tests for HIV-1 can be divided into virus culture techniques, antibody detection tests, antigen detection tests, PCR amplification tests, and immune function tests.

Testing for antibodies against HIV is accomplished by ELISA (enzyme immunoassay [EIA]), immunofluorescence assay (IFA), or Western blot. The ELISA/EIA for HIV is highly sensitive and specific. Concerns about false-positive results with ELISA testing can be alleviated by use of confirmatory tests. Because the positive predictive value of the test depends on the prevalence of HIV in the group being tested (low in the general population) and because of the tremendous medical, social, and psychological impact of a positive HIV antibody test, a confirmatory test for HIV infection is recommended when the ELISA is positive.

Additional concern exists over false-negative results, which can be seen in very early HIV infection and late-stage AIDS. A “window” exists early in infection, during which time HIV antibody cannot be detected but virus is present (plasma HIV-1 RNA, proviral DNA, culture, or antigen). During this window, the virus still can be transmitted. The HIV-1 testing algorithm recommended by the U.S. Public Health Service (USPHS) comprises initial screening with a United States Food and Drug Administration (FDA)-licensed EIA followed by confirmatory testing of repeatedly

reactive EIAs with an FDA-approved supplemental test (e.g., Western blot) or IFA (271). The diagnosis of HIV infection in adults requires that both ELISA/EIA and confirmatory test be positive (272).

Definitive diagnosis of HIV infection in infants requires use of assays other than the standard antibody assays used for adults (273). Virtually all infants born to HIV-infected mothers passively acquire maternal antibody and will test positive for up to 18 months of age (274). Uninfected infants lose maternally acquired antibodies, whereas infected infants remain antibody positive. Diagnosis of HIV infection in early infancy has relied (until recently) on two or more positive assays using viral culture, PCR, or p24 antigen test (203). Subsequently, detection of HIV proviral genome in PBMCs using PCR (DNA PCR) was shown to be a highly sensitive, specific, rapid, and cost-effective screening test for vertically transmitted HIV infection (275,276). The DNA PCR technique identifies 25% to 30% of infected infants at birth and the other 70% to 75% of infected infants by 1 month of age. Per the CDC, evaluation of an infant's infection status should begin within 48 hours of birth, with repeated evaluations at 1 to 2 weeks, and at 1, 2, and 6 months. Infants with a single positive DNA PCR result should have a follow-up blood specimen drawn immediately for confirmatory studies (DNA PCR and viral isolation) (272).

The confirmatory test most commonly used is the Western blot test. This method of gel chromatography isolates the protein in the viral core and envelope (p24 or gp41 bands). Thus, the Western blot test allows determination of the specific antigens against which antibodies are directed. In general, positive bands from two of the three major antigen groups, the *gag, pol,* or *env* region of the virus, are required for a positive test. The CDC criteria require the presence of at least two of the three bands, p24, gp41, or gp160/120, for a positive result. False-positive Western blot results are extremely uncommon (273). Indeterminate Western blot results do occur and are caused by incomplete antibody response to HIV or nonspecific reactions in sera of uninfected persons (273). Incomplete antibody responses may occur in persons recently infected with HIV who are seroconverting, persons with end-stage disease, and perinatally exposed infants who are seroconverting (i.e., losing maternal antibody) (273). Nonspecific reactions causing intermediate results occur more frequently in pregnant or parous women than in other individuals in low HIV seroprevalence groups (277,278). The IFA test, which uses HIV-infected T cells as antigen, is not widely used because of the time, expense, and expertise required. However, IFA can be used to resolve an EIA-positive, Western blot-indeterminate specimen (273).

Viral culture for HIV is expensive and slow (>1 month), and its sensitivity is unknown. Because of these characteristics, viral culture for HIV has not been used extensively in routine clinical care of HIV-infected persons. Moreover, special biocontaminant facilities are required for working with HIV. Several viral culture techniques are available. Peripheral blood mononuclear cells coculture for HIV-1 isolation was the technique originally used to establish HIV-1 as the etiologic agent of AIDS (279). It is estimated that this test, when performed appropriately, is positive in 95% to 99% of HIV-1 infected patients (280). Quantitative cell culture measures the relative amount of viral load within cells. Measurement of free infectious virus in plasma is another method to measure viral load (139,281,282).

Several methods and test kits have been developed for detection of HIV antigen. In general, these tests detect the p24 and gp41 antigens of HIV (283). Clearly, following

infection with HIV, the virus can replicate in the absence of detectable antibody response (283,284). In most individuals, this window lasts only a few weeks, but in rare instances HIV antigen has been detected for up to 6 to 4 months before seroconversion (283,284). The HIV antigenemia mirrors HIV-1 RNA levels and is biphasic: an initial high level prior to seroconversion and reappearance of antigen late in the disease process as the immune system is depleted. The introduction of monoclonal anti-p24 antibodies significantly increased the sensitivity of the p24 antigen assay, with levels as low as 7 to 10 pg/mL being detected. An additional modification, the acidified p24 antigen procedure, further enhanced the sensitivity of p24 antigen testing. Acidification of plasma disrupts the antigen-antibody complex and releases free p24 antigen for detection (285,286). This method was particularly useful for diagnosis of HIV infection in the newborn (*in utero* acquisition) prior to the availability of tests that measure HIV proviral DNA and HIV-1 RNA in plasma.

The introduction of PCR for detection of HIV was an important addition to our battery of HIV detection tests. The PCR is an amplification technique for viral DNA and allows rapid detection of small amounts of HIV (287,288). This technique can detect as few as one copy of HIV per 100,000 cells. Application of the PCR technique for early diagnosis of HIV infection of the newborn was a significant advance. In the case of HIV, proviral HIV-1 DNA, genomic RNA, and mRNA have all been amplified successfully. The major drawback to PCR is its phenomenal sensitivity; thus, very small amounts of contamination can result in false-positive results. Techniques have been developed to quantitate the amount of HIV proviral DNA and genomic RNA as measures of viral load (289,290). Competitive PCR techniques also have shown great promise. Extracellular HIV-1 RNA rises to high levels shortly after infection in adults (58,60,86,87,206) and in infants (291). Thus, the sensitivity of tests detecting HIV-1 RNA are excellent for diagnosis of acute and chronic HIV infection in adults and early diagnosis of perinatally acquired HIV infection (292). Steketee et al. (292) documented that plasma HIV RNA was detectable earlier and more reliably than HIV DNA in perinatal HIV infection.

Rapid HIV testing is now available; results can be available in 10 minutes (272,293,294 and 295). The sensitivity and specificity of these assays are comparable to those of ELISA/EIA (i.e., sensitivity 100%, specificity 99%) (272). However, the positive predictive value varies according to the prevalence of HIV infection in the population tested. Thus, the positive predictive value is low in low-prevalence populations, resulting in many false-positive results. As a consequence, results of reactive rapid HIV tests must be confirmed (272). The greatest utility of rapid HIV testing probably is among pregnant women in labor whose HIV status is unknown, especially in areas where the prevalence of HIV is high. Such an approach would identify those pregnant women whose infants might benefit from intrapartum and postdelivery administration of antiretroviral therapy (272). Similarly, rapid tests can be utilized on newborns to determine their HIV exposure. Consideration should be given to having rapid HIV testing available to patients in hospitals where the prevalence of HIV is high and the incidence of no prenatal care is high (272,293,294 and 295). A cost-benefit analysis by Stringer and Rouse (294) demonstrated that use of rapid HIV testing would be cost saving when the HIV prevalence is greater than 0.97%, treatment reduces vertical transmission by more than 5.8%, and the lifetime costs of pediatric HIV infection is greater than $33,625.

Epidemiology Of HIV Infection In Women

As of June 2000 in the United States, 124,911 women with AIDS had been reported to the CDC (4). Women account for 17% of all cumulative reported AIDS cases through June 2000, a substantial increase from 8% of cases reported from 1981 to 1987 (296). Women have the fastest rate of increase in HIV infection in the United States. In the year ending June 2000, women represented 24% of the AIDS cases reported to the CDC (4,297). Figure 10.17 shows the growing role of women in the AIDS epidemic in the United States. Acquired immunodeficiency syndrome currently is the third leading cause of death in all women in the United States and the leading cause of death in African-American women (48). In the United States, AIDS, especially heterosexually acquired, occurs disproportionately in women of color, with more than 80% in African-American or Hispanic women (296,297 and 298). On a global basis, women account for nearly 50% of the more than 53 million adults estimated to have been infected with HIV as the new millennium began (32). UNAIDS estimates that more than 6,500 new cases of HIV infection are diagnosed in women each day worldwide (32).

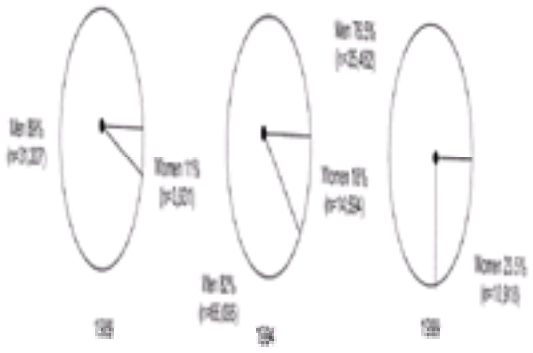


FIGURE 10.17. Gender distribution of AIDS cases reported in 1989, 1994, and 1999.

Worldwide heterosexual transmission is the predominant mode of HIV transmission (32). In the United States, MSM remains the largest category of transmission; among women, heterosexual transmission is the largest group (39%), followed by IDU (27%) (4). After reclassification of the “not reported or identified” cases, heterosexual contact accounts for more than 60% of AIDS cases currently reported in women (4). Newman (48) reviewed the factors underlying the increased incidence of HIV infection in women. The factors driving the HIV epidemic in women are predominantly socioeconomic and include (i) lack of power to negotiate condom use with partners; (ii) financial dependence on partner; (iii) history of childhood and adult sexual and physical abuse; and (iv) high poverty and unemployment rates, which force women to trade sex for food, housing, and money.

Newman and Wofsy (296) noted that the most alarming trends of heterosexual transmission are occurring in young women. The largest increases in AIDS incidence reported in the mid 1990s were seen in women who had been 14 to 18 years old in

the mid to late 1980s when they presumably were infected (299). Two factors contribute to this occurrence. (i) These young women tend to have partners who on average are 5 years older, which may exacerbate their inability to negotiate with sex partners for condom use (299,300 and 301). (ii) The occurrence in young adolescents of cervical ectopy (where columnar epithelial cells of the endocervix are more exposed), which is a normal physiologic state in this age group, allows for more efficient transmission of HIV (296). The CDC estimates that women currently represent approximately 40% of new HIV infections reported in the United States. In some inner cities, the CDC estimates that as high as 60% of new HIV cases occur in women (302).

Progression of Disease

Several initial studies suggested that survival time was shorter for women diagnosed with AIDS than for men regardless of the risk group or race (302,303,304 and 305). However, more recent investigations refute the notion that women have increased morbidity and mortality as a result of gender. They attributed this observation to other factors, including younger age, delays in diagnosis with resultant lower levels of $CD4^+$ counts, lower use of antiretroviral therapy, and less access to health care (306,307,308 and 309). Studies by Creagh-Kirk et al. (310), Ellerbrock et al. (311), and Chaisson et al. (312) failed to identify any difference in progression of HIV disease and/or survival by gender.

Additional studies support the concept that gender differences do not result in faster progression of HIV infection and worse survival in women (308,313,314 and 315). Flanigan et al. (313) noted no differences in decline of $CD4^+$ cell counts between women and men. In a large multisite community-based clinical trial, HIV-infected women were demonstrated to have a similar risk for disease progression as men and similar rates of new opportunistic infections (308). Two large Italian studies found no significant differences in the progression of AIDS by gender (314,315).

The overwhelming consensus from these investigations holds that there is no difference between women and men in HIV disease progression after controlling for other variables such as viral load, CD4 count, age and date of seroconversion, and access to current medical management (298). Clearly, the most important predictors of survival and/or progression are viral load, CD4 count, and the specific AIDS-defining diagnosis, rather than gender (58,60,87,300,316).

It has been suggested that viral load levels are different in women and men with similar $CD4^+$ T-cell counts (48). The CDC demonstrated that the viral load in women was 57% lower for patients with $CD4^+$ cell counts greater than 500/mL, 48% lower for counts between 200 and 499 m/L, and 40% lower for counts less than 200/mL, but gender was not associated with either time to an AIDS-defining opportunistic infection or time to death. Thus, the CDC, the Department of Health and Human Services, and the International AIDS Society-USA do not recommend changing antiretroviral treatment guidelines based on gender for women (48).

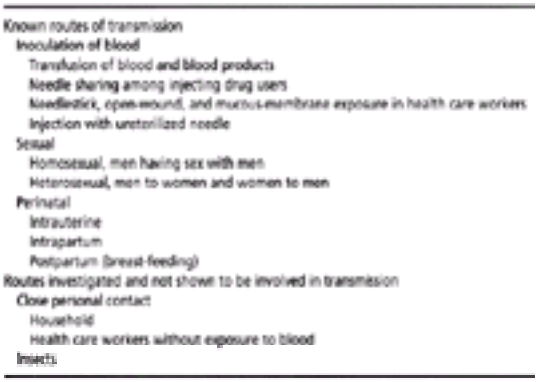
In addition, the CDC assessed the causes and rates of mortality in HIV-infected women from April 1993 through December 1998 (48). Among verifiable causes of death, 16% died of an AIDS-defining illness and 40% of HIV-related disease. Among the remaining 44%, one third of deaths was associated with IDU (e.g., endocarditis,

sepsis, hepatitis). Unfortunately, only 24% of women with $CD4^+$ cell counts less than 200/mL received potent antiretroviral therapy. This lack of current state-of-the-art highly effective antiretroviral therapy was a strong predictor of mortality when the viral load was greater than 10,000 HIV RNA copies/mL and the $CD4^+$ cell count was less than 200/mL (48).

Transmission of HIV

There have been three subepidemics (waves) of HIV infection in the United States. The initial subepidemic of HIV spread occurred primarily in the homosexual community. The second involved intravenous drug users, and the third involved heterosexual partners of IDUs, bisexual men, and other HIV-infected men. It is this third wave that will impact on providers of health care for women. More than 80% of women with AIDS are of childbearing age and are a major source for vertical transmission of HIV infection to their infants (4). In addition, the most common route of transmission of AIDS to women is heterosexual contact (4,317). As described previously, heterosexual spread plays an increasing role for transmission of HIV in the United States and is a major risk factor for women. Worldwide heterosexual transmission is the predominant mode for HIV transmission.

Interestingly, the possible routes of transmission for AIDS were recognized before the etiologic agent (HIV) was even identified (133). The presence of AIDS in such diverse groups as homosexual males, intravenous drug abusers, recipients of blood or blood products, heterosexual partners of AIDS patients, Haitians, and Africans suggested that AIDS was due to transmission of an infectious agent by sexual contact, blood or blood products, and the vertical perinatal route (Table 10.16) (133).


Known routes of transmission
- Inoculation of blood
  - Transfusion of blood and blood products
  - Needle sharing among injecting drug users
  - Needlestick, open-wound, and mucous-membrane exposure in health care workers
  - Injection with unsterilized needle
- Sexual
  - Homosexual, men having sex with men
  - Heterosexual, men to women and women to men
- Perinatal
  - Intrauterine
  - Intrapartum
  - Postpartum (breast-feeding)

Routes investigated and not shown to be involved in transmission
- Close personal contact
  - Household
  - Health care workers without exposure to blood
- Insects

TABLE 10.16. TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Human immunodeficiency virus can be sexually transmitted by homosexual and heterosexual activity. Whereas homosexual sexual transmission has been the leading route for HIV infection in the United States, heterosexual sexual transmission is the major route for HIV infection worldwide (4,43,48,133,296,297 and 298,317,318). However, heterosexual sexual transmission is attaining increasing

importance in the United States, where the proportion of AIDS cases attributed to heterosexual transmission is increasing at a more rapid rate than other risk categories (4,296,297 and 298). In 1987, only 1.7% of adult AIDS cases were attributed to heterosexual transmission; in 1994, heterosexual transmission accounted for 10% of cases; and in 1999, heterosexual transmission was responsible for 16% of cases. For women, the increasing importance of heterosexual transmission is even more dramatic, with an increase from 27% of 1987 cases to greater than 60% of female AIDS cases in 1999 (4).

Haverkos and Edelman (318) provided an extensive review of the epidemiology of AIDS in heterosexuals at the end of the 1980s. They identified risk variables that exist for AIDS in women. These risk variables include (i) geographic region (eastern seaboard); (ii) intravenous drug use and needle sharing; (iii) age; (iv) race/ethnicity (African-American and Hispanic); and (v) urban residence. The CDC has reported that the highest HIV seroprevalence in women occurs in metropolitan areas, especially among intravenous drug users (319). The rates of AIDS are about ten times higher in African-American and Hispanic women (319).

Transmissibility

The risk for acquiring HIV infection from a single or even multiple sexual acts with an infected individual is not known. There is general agreement that HIV is less easily transmitted than other STD organisms, such as *Neisseria gonorrhoeae, Chlamydia trachomatis,* and *Treponema palladium.* Worldwide, unprotected heterosexual intercourse is the major risk factor for HIV infection in women and adolescents (298). Reviews on the transmission of HIV have reported that the overall rate of seropositivity in steady heterosexual partners of individuals with AIDS ranged from 7% to 68% (133). Male-to-female transmission of HIV is relatively more efficient than female-to-male transmission (48,296,320,321 and 322). In this vein, Padian and coworkers (322) documented that the risk of male-to-female transmission (19%) was 17 times higher than the risk of female-to-male transmission. A lower but same direction risk was found by Nicolosi and coworkers (323) in an Italian cohort of 730 discordant couples in stable relationships, with a twofold increased risk associated with male-to-female transmission. In a study that prospectively followed HIV discordant couples since 1985, Padian et al. (324) found that 68 (19%) of 360 female partners of HIV-infected men became infected versus 2 (2.4%) of 82 male partners of HIV-infected women. Additional studies confirmed that the male-to-female transmission is more efficient than female-to-male transmission (325,326,327 and 328).

Risk factors that are associated with heterosexual transmission have been suggested. These factors include lack of condom use, presence of other STDs (ulcerative and nonulcerative), advanced disease state (according to $CD4^+$ cell count, viral load, or AIDS diagnosis), intrauterine contraceptive use, and cervical ectopy (296,298,324,329,330,331,332,333 and 334). The role of oral contraceptives in facilitating transmission to, or acquisition of, HIV infection by women is uncertain (246,298,335,336). As noted by Daly et al. (335), there are theoretical explanations for how hormonal contraceptive use could increase the risk for HIV infection. These explanations include increased cervical ectopy, local effects of progesterone within the vaginal epithelium, and changes in cervical mucus. Most interesting is the rhesus monkey model of Marx et al. (337), who noted that progesterone implants resulted in vaginal wall thinning and a nearly eightfold increased risk of acquiring simian

immunodeficiency virus (SIV). These authors proposed that thinning of the vaginal epithelium resulted in loss of the physical barrier of the vaginal wall, which exposed and rendered dendritic (Langerhans) cells in the vaginal epithelium more susceptible to HIV infection. In addition, progesterone may act to down-regulate cell-mediated immune effectors (cytotoxic $CD8^+$ lymphocytes) (338). Mostad et al. (339) demonstrated that both medroxyprogesterone acetate (Depo-Provera) and oral contraceptives were associated with increased viral shedding from the cervix, even after controlling for low $CD4^+$ cell counts.

Peterman et al. (340) initially suggested the possibility that transmission of HIV may be determined by variation among strains of the virus. More recent investigations demonstrated that specific HIV subtypes (E and C) replicate more readily in dendritic (Langerhans) cells than subtype B (341,342). This finding fits the epidemiologic data showing that heterosexual transmission is increased in Thailand and India, where subtypes E and C, respectively, are common (296). On the other hand, subtype B predominates in North America, where heterosexual transmission is less common. Viral phenotypic characteristics also have been associated with transmission risk; most primary HIV infection occurs with acquisition of nonsyncytium-inducing phenotypes, especially in sexual or vertical transmission (296). The nonsyncytium-inducing strains of HIV appear to be more common in IDU women and heterosexual men than in MSM (343). The diversity of HIV populations in newly acquired, heterosexually transmitted infections has been the focus of study (344,345). Poss et al. (344) noted increased heterogenous HIV-1 virus populations in infected cells from genital secretions and peripheral blood in women compared to the situation in homosexual males or perinatal HIV transmission, where a single dominant genetic variant is present. Long and coworkers (345) confirmed this finding. They demonstrated that women were often infected by multiple virus variants, whereas men were not (345). Moreover, they noted that heterogeneous virus was present in women before seroconversion and was derived in each woman from a single index case. This latter finding suggests that HIV-1 diversity was the result of transmission of multiple variants (345). Thus, it appears that women typically are infected by multiple HIV variants from their partners, whereas men usually are infected by only a single viral genotype (344,345). Infants appear to be similar to men in that they also are infected with a single genotype of HIV (346). Long and coworkers (345) noted that the diverse virus population in women early after infection is of concern. If diversity reflects an absence of selectivity, it is possible that acquisition of more virulent viruses is favored (347). Alternatively, early infection by multiple variants elicits a broader HIV-1–specific immune response that could be effective in keeping the virus population under control for a longer period of time (345).

Not only has the role of viral characteristics in the risk of sexual transmission been assessed, but the role of viral load also has been the focus of investigative interest (298). Generally, the viral load in semen correlates with the viral load in plasma (298). In individual patients, substantial differences in viral loads can be present in different body compartments; such differences could affect the risk of sexual transmission (298). Pedraza and coworkers (348) demonstrated that transmission in heterosexuals was associated with rapidly replicating virus (in tissue culture) and increased plasma viral load (>15,000 HIV-1 RNA copies/mL). Administration of potent antiretroviral therapy substantially reduces HIV viral load in semen and vaginal secretions (348,349,350 and 351). Although such a decrease could reduce the risk of sexual transmission, as noted by Newman and Wofsy (296), antiretroviral therapy should not be considered an effective means of preventing sexual

transmission of HIV.

Until recently, it has been unclear whether differences existed between men and women for the viral load of HIV-1 RNA in plasma. Several studies demonstrated lower levels in women than men, after controlling for $CD4^+$ lymphocyte counts (352,353,354,355 and 356). On the other hand, no difference was noted in other studies (357,358). In men, the viral load of HIV-1 RNA following seroconversion is a strong independent predictor of the risk of progression to AIDS (244,257,266,267,359,360,361 and 362). As a result of these investigations, viral load has formed the basis on which the current guidelines for initiation of antiretroviral therapy, which apply similarly to women and men, have been formulated (363,364). However, the relation between initial viral load in women and the risk of progression to AIDS had not been studied until the report by Sterling et al. (365). These authors assessed the viral load and $CD4^+$ lymphocyte count longitudinally over a 10-year period following seroconversion in 156 male and 46 female IDUs. The median initial viral load was significantly higher in men (50,766 copies HIV-1 RNA per milliliter) than in women (15,103 copies HIV-1 RNA per milliliter) ($p < 0.001$). This difference in viral load persisted for several years after seroconversion. In contradistinction, the median $CD4^+$ count did not differ significantly by gender (men 659; women 672). Furthermore, the risk of progression to AIDS did not differ significantly by gender. This study identifies a key issue: given that current recommendations for initiation of antiretroviral therapy use a level of 20,000 copies of HIV-1 RNA, only 37% of women as compared to 74% of men would have been eligible for therapy at the first visit after seroconversion ($p < 0.001$). As noted by Sterling et al. (365), it would be expected that women, with a lower viral load, would be at a lower risk for progression to AIDS. However, as discussed previously, multiple studies found that the risk for progression to AIDS does not differ between men and women. The mechanism explaining why women with a lower viral load progress to AIDS at the same rate as men is an enigma that requires further investigation.

Sexually transmitted diseases, especially those that manifest as genital ulcers, have been strongly associated with an increased risk for HIV infection (149,150 and 151,325,328,366,367,368,369,370,371,372,373 and 374). Initially, an association was demonstrated between sexually transmitted genital ulcer disease and HIV infection. Studies in Africa demonstrated an association between HIV infection and genital ulcer disease in heterosexual populations (149,150). Stamm and coworkers (151) demonstrated that genital ulcerations also are an important risk factor for acquisition of HIV infection in homosexual men in the United States. Genital ulceration could facilitate acquisition and/or transmission of HIV in two ways (151). First, ulceration provides a more accessible portal of entry or exit for HIV. Second, the immune and inflammatory response to genital ulcers (especially HSV and syphilis) results in activated macrophages and stimulated T_4 lymphocytes. Not only are such stimulated cells more susceptible to HIV *(in vitro)* (375), but such stimulation of latent HIV-infected T lymphocytes results in activation, and increased shedding, of HIV (376). In addition, nonulcerative STDs have been associated with an increased risk for HIV infection (367,370). In a multivariate analysis of risk factors for HIV seroconversion among prostitutes in Kinshasa, Zaire, Laga et al. (367) reported an increased risk for HIV transmission in women infected with gonorrhea (odds ratio [OR], 4.8; 95% confidence interval [CI], 2.4–9.8), chlamydia (OR, 3.6; 95% CI, 1.4–9.1), and trichomoniasis (OR, 1.9; 95% CI, 0.9–4.1). Moderate increases with gonorrhea (1.4) and chlamydia (1.4) also were seen among

HIV-infected prostitutes in Amsterdam (370). Tumwesigye et al. (374) noted in a twofold increased risk of cervicitis in HIV-infected women compared to a non–HIV-infected group.

Additional studies have demonstrated that genital tract infections increase the shedding of HIV-1 (376,377). Cohen and coworkers demonstrated that the semen of men with urethritis (gonococcal more so than chlamydial) contained higher levels of HIV-1 RNA than HIV-infected men without urethritis (376a). Similarly, Gyhs et al. (377) reported increased levels of cervicovaginal shedding of HIV in women coinfected with STDs. In both of these studies, treatment of STD (nonulcerative and ulcerative) reduced shedding of HIV, although shedding was not eliminated (376,377). As a consequence of this increased HIV shedding, the likelihood increases that genital secretions will contain viral load of HIV required for transmission (378). Contrary to the situation where HIV-infected women are not coinfected with other STDs and where the rate of female-to-male transmission is less efficient, if women have another STD, female-to-male transmission is as likely as male-to-female transmission (379,380). As noted by Hitchcock and Fransen (378), in HIV-negative partners, STDs increase the amount of susceptible tissue and the infectious dose is lowered.

An association of HIV infection and BV has been reported in both cross-sectional and longitudinal studies (381,382,383,384 and 385). In the cross-sectional studies, women with BV had a higher prevalence of HIV infection (381,382 and 383). Cohen et al. noted a significant association of BV and HIV seropositivity (OR, 2.7; 95% CI, 1.3–5.0) in female commercial sex workers in Thailand. In the Raki area of Uganda, Sewankambo and coworkers (381) reported that women with moderate or severe BV were at increased risk for HIV infection with odds ratios of 1.5 (1.18–1.89) and 2.08 (1.48–2.94), respectively. In the United States, Royce et al. (383) noted that as vaginal flora BV score increased (normal to abnormal), the prevalence of HIV increased. The relative risk of HIV infection was 1.5 (95% CI, 0.2–12.9) with intermediate flora and 4.0 (95% CI, 1.1–1.49) for abnormal flora (383). Two longitudinal studies demonstrated that women with BV have an increased risk to acquire HIV (384,385). Taha et al. (384) reported that pregnant women with clinical BV in Malawi had an increased risk for HIV-1 seroconversion during pregnancy and in the postpartum period. Antenatal seroconversion odds ratio was 3.7 (p = 0.04) and postpartum adjusted rate ratio was 2.3 (384). Martin and coworkers (385) conducted a prospective cohort study examining the relationship between vaginal colonization with lactobacilli, BV, and acquisition of HIV. During follow-up, absence of vaginal lactobacilli was associated with an increased risk for acquiring HIV-1 infection (hazard ratio [HR], 2.0; 95% CI, 1.2–3.5). Presence of abnormal flora on Gram stain also was associated with increased risk for HIV-1 acquisition (HR, 1.9; 95% CI, 1.1–3.1) (385). Potential mechanisms to explain the association of BV and HIV include (i) peroxide-producing lactobacilli predominate in the normal vaginal flora and maintain a low pH; (ii) peroxide-producing lactobacilli demonstrate viricidal effects on HIV-1 (386); (iii) combining peroxidases and halide ion (both present in the vagina) with peroxide enhances the viricidal activity from 50% (peroxide alone) to nearly 100% (386); and (iv) low vaginal pH (as seen with normal flora) inhibits $CD4^+$ lymphocyte activation and may reduce the number of target cells for HIV-1 in the vagina (387).

Two important, community-based intervention trials were performed to assess the impact of STD prevention and control on HIV infection rates (148,388). The initial

study in Mwanza, Tanzania, focused on enhanced syndromic diagnosis and treatment of symptomatic STDs in an area where the HIV epidemic was in its early stages, with an estimated HIV seroprevalence of 4% (148). In this study, HIV incidence was reduced by 42% after 2 years (148). The second study focused on community-based treatment of all members, including those with symptomatic and asymptomatic STDs in the Raki district of Uganda, an area where the AIDS epidemic was well established, with 16% of the study population HIV seropositive (388). The Raki study found that HIV infections were not prevented by the intervention (388). In their commentary on the Raki study, Hitchcock and Fransen (378) point out that although STD interventions are effective early in the AIDS epidemic, once the epidemic has matured beyond phase 1 (rapid infection of very susceptible infection), short-term STD prevention and control probably will have very little impact on the AIDS epidemic.

Transmission of HIV via blood occurs by several mechanisms. As of June 30, 2000, less than 1% of adults with AIDS in the United States acquired HIV infection from transfusion of blood or blood products (4). Although whole blood, blood cellular components, plasma, and clotting factors have been shown to transmit HIV infection, no products prepared from immunoglobulin, albumin, or plasma protein fraction have been demonstrated to do so (133). Individuals at risk for transfusion-associated HIV infection are those who received blood between 1978 and April 1985, when screening donated blood and plasma for HIV antibody was instituted. Such screening and heat treatment of clotting-factor concentrates have significantly reduced the risk of acquiring HIV via transfused blood products. It is estimated that the risk of acquiring HIV infection from a transfused unit of blood is between one in 100,000 and one in 1,000,000 (133).

Second, parenteral inoculation of blood may transmit HIV. Fortunately, the parenteral route is associated with a very low risk of transmission (389). This low risk probably is due to the very small inoculum of blood associated with single needle-stick injuries. The risk of occupational HIV transmission has been assessed in prospective studies of exposed health care workers (389,390,391,392,393,394,395,396,397,398,399 and 400). Pooled data demonstrate that the average risk of HIV transmission associated with needle punctures or similar percutaneous injuries is 0.32% (21 infections following 6,498 exposures; 95% CI, 0.18%–0.46%) (399). For mucocutaneous transmission, the estimated risk is 0.09% (one infection following 2,885 exposures through mucous membranes or nonintact skin) (396). These studies show that no infection occurred from (i) routine (nonparental) contact with HIV-infected patients; (ii) aerosolization or airborne droplets; (iii) cutaneous exposure involving intact skin; or (iv) contact with contaminated environmental surfaces or fomites. Thus, it appears that only needle sticks with blood from HIV-infected individuals have been associated with infection in the study of health care workers. This risk is very low with exposure to patients known to be infected with HIV. Blood or bloody fluid has been implicated as the source of exposure in all infections occurring in health care providers (391). Even though other body fluids (saliva, tears, urine) contain virus, the titer of HIV in these fluids usually is much lower than in blood or semen. Cutaneous exposure involving intact skin has not been linked to HIV infection in any setting (389). Thus, the overall risk to health care workers in the United States is likely to be even lower.

As reviewed by Gerberding (389), the factors that influence infectivity in health care workers exposed to blood or bloody fluids from HIV-infected patients have not been

completely defined. However, the inoculum of virus transmitted during exposure is very important (389). In 1997, the CDC reported the results of a case-control study of HIV seroconversion in health care workers after percutaneous exposures (Table 10.17) (401). Deep intramuscular penetrations, large-bore hollow needles, and injections of blood are the factors associated with most of the needle-stick injuries that result in occupationally acquired HIV infections. Deep punctures (i.e., skin penetrated, resulting in spontaneous bleeding), injuries caused by devices visibly contaminated with blood and injuries associated with devices that had entered a blood vessel were found to be independent factors associated with risk for acquisition of HIV (401). When the source patient has preterminal AIDS (circulating levels of HIV-1 RNA are at their highest) there is a sixfold increased risk for acquiring HIV infection (401).

Risk Factor	Odds Ratio
Deep injury	15.0
Visible blood on sharp device	6.2
Device used to enter blood vessel	4.3
Source patient with terminal acquired immunodeficiency syndrome	5.6
Postexposure zidovudine treatment	0.19

From Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposures. *N Engl J Med* 1997;37:1485.

TABLE 10.17. FACTORS INDEPENDENTLY ASSOCIATED WITH PERCUTANEOUS INJURY TRANSMISSION RISK BY LOGISTIC REGRESSION ANALYSIS

Provider-to-patient transmission of HIV could occur by direct inoculation of blood or other infected body fluids or through use of contaminated materials or equipment (389). To date, only a single case of HIV infection has been attributed to transmission during a surgical procedure, although the exact mode has not been determined. Another provider-to-patient HIV transmission has been attributed to a cluster of six patients infected by a single infected dentist. It is unclear if this transmission was due to faulty procedures or was intentional (389).

The third method (and by far the most difficult to manage) for transmission by blood is that via intravenous drug use. As of June 2000, 31% of AIDS cases in the United States occurred in IDUs, with 25% in persons for whom IDU is the only risk factor (4). Among women with AIDS, 41% are IDUs. The importance of IDU is dramatized by the recognition that IDUs are the largest pool of HIV-infected heterosexuals in the United States and that IDUs and partners of male IDUs are the major source of perinatal AIDS. The major risk factor for transmission of HIV in association with IDU is sharing of unsterilized needles and syringes contaminated with HIV-infected blood.

Three routes for mother-child transmission of HIV have been proposed. These are (i) *in utero* transplacental transmission from maternal circulation (404,405 and 406); (ii)

intrapartum transmission during labor and delivery by inoculation or ingestion of blood or other infected fluids, such as amniotic fluid, or genital secretions; and (iii) postpartum transmission via ingestion of infected breast milk (407).

The timing of perinatal transmission has not been clearly delineated. Wara and Dorenbaum (408) hypothesized that the timing of transmission and the viral burden in the newborn determine the time of onset of clinical disease and the rate of clinical progression in children. These authors suggested that the earlier HIV is transmitted from mother to infant and the larger the viral burden in the newborn period, the greater the likelihood that clinical disease will progress more rapidly (408). Moreover, a bimodal model of *in utero* and intrapartum transmission appears to exist (409). Bryson et al. (409) suggested that infants infected *in utero* have virus detected by culture or PCR within 48 hours of birth. The presence of *in utero* transmission is supported by studies demonstrating HIV-1 in fetal tissues as early as 8 weeks' gestation (410,411) and in fetal thymus tissue as early as 15 weeks (412). According to the Institute of Medicine, at most 25% to 30% of perinatal HIV transmission occurs *in utero* (413,414 and 415). Indirect evidence suggests that 70% to 75% or vertical transmission of HIV occurs intrapartum (414,415 and 416).

The rate of perinatal transmission of HIV varies by geographic region. This risk will be discussed in detail in the next section. Briefly, in the United States and western Europe prior to widespread use of antiretroviral therapy, transmission rates ranged from 14% to 33% (272). In the developing world, rates as high as 43% have been reported (272).

Clinical Manifestations of HIV Infection in Women

Factors that may influence the clinical presentation of HIV infection and the response to therapy in women were reviewed by Newman and Wofsy (296). These factors include altered pharmacokinetics of drugs secondary to gender or interactions between commonly used drugs and antiretroviral agents, and differences in the immune system. In general, the clinical manifestations of HIV disease are similar for men and women (298). However, there are gender differences related to the occurrence of specific AIDS-defining opportunistic infections or malignancies. For example, HIV-infected women have lower rates of Kaposi sarcoma than men, and they have higher rates of recurrent bacterial pneumonia with encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*) (417,418). In addition, increased rates of specific diseases of the female genital tract related to HIV infection are seen in HIV-infected women (298), including higher rates of cervical dysplasia with accelerated progression to invasive cervical cancer (419,420 and 421) and recurrent vulvovaginal candidiasis (422,423).

Carpenter and coworkers (424) reported the initial clinical manifestations of HIV infection in a cohort of 200 HIV-infected women. Among the 117 symptomatic patients, they noted vulvovaginal candidiasis in 43 (37%), lymphadenopathy in 17 (14.5%), bacterial pneumonia in 15 (13%), acute HIV infection in 8 (7%), and constitution symptoms (e.g., unexplained weight loss >10 pounds, diarrhea ³4 weeks) in 8 (7%). The remaining 26 symptomatic women had syndromes suggestive of HIV infection, including thrush, tuberculosis, hairy leukoplakia, herpes zoster, PCP, AIDS encephalopathy, and CMV retinitis. Esophageal candidiasis was the most common AIDS-defining manifestation in 34%; PCP was the AIDS-defining illness in only 20% of HIV-infected women (424). Creagh et al. (425) reported that, in

French women, esophageal candidiasis was a more common AIDS-defining manifestation than PCP. Similarly, Sha and coworkers (418) documented that esophageal candidiasis (42%) was the most common AIDS-defining illness in HIV-infected women, followed by PCP (35%). Over time, esophageal candidiasis accounted for 54% of all AIDS diagnosis in this group of women (418). These findings are in distinct contradiction to national data in which PCP was the most common AIDS-defining illness in men. However, other investigations have failed to confirm this finding and have not noted any gender differences in the frequency of esophageal candidiasis or other AIDS-defining opportunistic infections (426,427,428 and 429). Other opportunistic infections commonly seen in HIV-infected women include CMV, recurrent mucocutaneous HSV, mucocutaneous candidiasis, toxoplasmosis, and tuberculosis (417).

Early in the AIDS epidemic, the increased occurrence of certain malignancies associated with HIV infection and immunosuppression was apparent (296,298). It is estimated that 40% or more of HIV-infected persons have cancer, either as a cause of mortality or morbidity (430,431). The malignancies most commonly associated with this morbidity/mortality in HIV-infected women include (i) non-Hodgkin lymphoma (NHL); (ii) Epstein-Barr-virus–associated tumors; (iii) Kaposi sarcoma due to human herpesvirus 8; and (iv) cervical intraepithelial neoplasia (CIN) due to human papillomaviruses (HPVs) (296,298,430,431). Increases in risk for Kaposi sarcoma and NHL in HIV-infected women have been reported (432). The AIDS-related risk for NHL is approximately the same across all HIV risk groups, and no gender difference has been noted (298,433). In contrast, although Kaposi sarcoma is present frequently in MSM, it is found in less than 2% of women as an AIDS-defining diagnosis (296). However, studies from Africa, the Caribbean, and Europe demonstrated that Kaposi sarcoma, as a first AIDS-defining illness, is present as frequently in men and women IDUs and heterosexuals (434,435 and 436). There is not a lower incidence or severity of Kaposi sarcoma in pregnant women (437).

Human papillomaviruses, CIN, and associated cancers appear to behave differently in HIV-infected women, especially as cell-mediated immunity is impaired. Human papillomaviruses and cervical neoplasia are discussed in the “Gynecologic Aspects of HIV Infection” section.

Transmission of HIV depends on both the infectiousness of the index case (438) and the susceptibility of the exposed host (327,439). The virologic factors required for transmission of HIV include (i) certain viral quasi-species appear to be favored (207); (ii) different viral subtypes (clades) found in various geographic areas may be transmitted with variable efficiency (440); and (iii) the viral envelope has an important role in determination of transmissibility (441). As reviewed by Cohen and coworkers (442), susceptibility of individuals to HIV infection depends on both lack of immunity in the exposed host and lack of genetic resistance. As discussed previously, persons with mutations in chemokine cell receptors demonstrate resistance to HIV infection (95,443).

Cofactors that amplify HIV transmission secondary to increasing the infectiousness of index cases or susceptibility of the exposed host have been described (443). Cohen et al. described (442) cofactors that cause inflammation of genital tract mucosa as the most important for transmission of HIV. Thus, untreated STDs may

increase both the infectiousness and susceptibility to HIV (372,444).

HIV Infection In Pregnancy

As discussed previously, an increasing percentage of AIDS patients and HIV-infected patients in the United States are women. More than 85% of these women are of reproductive age. Nearly 90% of pediatric AIDS cases are presumed to have acquired HIV infection perinatally from their mothers. Nearly 100% of new pediatric AIDS cases are acquired perinatally. This increasing infection rate in women and the increasing risk for perinatal transmission demonstrate that we will continue to be faced with the challenge of providing health care to pregnant women infected with HIV.

As documented by the CDC, the number of reported cases of perinatally acquired AIDS rose rapidly, in parallel with increases in the number of HIV-infected women, in the late 1980s and early 1990s, reaching a peak in 1992. Subsequently, a decline in perinatal AIDS cases has occurred (Fig. 10.10) (445). The decline in perinatally acquired AIDS in the United States has occurred despite a situation in which women have increasingly shouldered the burden of HIV disease. Women accounted for 18% of cumulative AIDS cases in the United States as of 1999 and accounted for 23% of new AIDS diagnoses and 32% of newly reported HIV diagnoses in the United States (446). An estimated 120,000 to 160,000 HIV-infected women are living in the United States (447).

From 1989 to 1994, an estimated 6,000 to 7,000 infants were born to HIV-infected women each year. By 1995, more than 16,000 children infected with HIV via the perinatal route had been born (448,449). Pediatric AIDS cases are concentrated along the eastern seaboard of the United States, especially in the New York City metropolitan area, with New York, New Jersey, and Florida accounting for approximately 50% of cases (450). The District of Columbia (6.3/10,000 births), New Jersey (4.3/10,000 births), Connecticut (3.8/10,000 births), and Maryland (3/10,000 births) have the highest incidence rates (450).

Lindegren et al. (451) reviewed the trends in perinatal transmission of HIV/AIDS in the United States. These authors reported an 80% decline in the number of perinatal AIDS cases from 1992 to 1997 and a 69% decrease in the rates of AIDS among infants (per 100,000 births) from 8.9 in 1992 to 2.8 in 1996, but only a 17% decline in births to HIV-infected women from 1992 (n = 6,990) to 1995 (n = 5,797) (451). In 1994, the Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076) demonstrated that ZDV, when administered to selected HIV-infected (mild) pregnant women and their newborns, reduced perinatal transmission by two thirds (452,453). This dramatic reduction in transmission resulted in the USPHS recommendation in August 1994 for the use of ZDV to reduce perinatal transmission of HIV (55) and in July 1995 for routine HIV counseling and voluntary prenatal testing of pregnant women for HIV infection (56). The percentage of perinatally exposed children born from 1993 to 1997 whose mothers were tested for HIV before delivery increased from 70% to 94%, and the percentage receiving ZDV increased from 7% to 91% (451). The dramatic decline in AIDS incidence among infants was associated with an increased use of ZDV to prevent perinatal transmission of HIV and reflected the tremendous success with which the PHS guidelines were implemented by health care providers for pregnant women (451).

Worldwide, a different picture exists. UNAIDS estimates that 1.2 million children were living with HIV-1 infection at the end of 1999, and an additional 3.6 million children had died (454). An estimated 2.4 million HIV-infected women give birth annually, and 1,600 infants acquire HIV-1 infection every day (455).

As noted by Mofenson and McIntyre (455), two perinatal epidemics exist. In more developed countries, integration of prenatal HIV counseling and testing programs into an existing antenatal infrastructure, availability of effective antiretroviral prophylaxis, and access to infant formula have resulted in new perinatal HIV infections becoming rare. In contradistinction, in less developed countries where antenatal care is limited, testing programs are almost nonexistent, effective interventions are not implemented, and prevention of transmission via breast-feeding while maintaining adequate infant nutrition is a major dilemma, vertical transmission of HIV from mother to infant remains a crisis.

Initial attempts to assess the seroprevalence of HIV infection in pregnant women yielded a wide range of seropositivity. In 1987, the CDC reported preliminary results from surveys and studies of HIV antibody prevalence in selected groups of pregnant women (456). They reported that HIV seroprevalence ranged from 0.0% to 1.7% in prenatal patients, 0.4% to 2.3% at the time of delivery, and 9.4% to 29.6% in pregnant IDUs. Several large-scale statewide screening programs using newborn heel-stick samples were performed in an attempt to determine the seroprevalence of HIV in the general population (457,458). Anonymous testing of newborn specimens in Massachusetts revealed an overall seropositivity of 0.21%. In New York, the overall HIV seroprevalence was 0.66%, ranging from 0.16% in upstate New York to 1.25% in New York City. To monitor the prevalence of HIV infection in women delivering infants in the United States, an anonymous national HIV serosurvey (Survey of Childbearing Women) was conducted from 1988 to 1994 using residual dried-blood spot specimens collected routinely from newborns for metabolic screening (136). A weighted, nationwide estimate of HIV infection prevalence was 1.6 per 1,000 childbearing women (136). The estimates of HIV prevalence in childbearing women in the United States remained stable from 1988 to 1994 (136). HIV prevalence in childbearing women varies by geographic area, with the highest prevalences in 1994 reported (per 1,000 women) in the District of Columbia (6.9), New York (5.2), Puerto Rico (4.7), and Florida (4.6) (136).

Several areas of concern have emerged regarding HIV infection in pregnancy. These concerns include the (I) effect of pregnancy on HIV infection; (ii) effect of HIV infection on pregnancy outcome; (iii) risk of vertical transmission from infected mother to her offspring; (iv) management of HIV-infected pregnant women; (v) prevention of pediatric AIDS; and (vi) early diagnosis of newborn HIV infection.

Effect of Pregnancy on HIV Infection

There has been concern that pregnancy may accelerate the progression of HIV infection from the asymptomatic stage to symptomatic HIV infection and AIDS (459). Three lines of evidence have been used to suggest that such an occurrence is biologically plausible. Pregnancy has been associated with decreased levels of T_4 cells (460) and decreased lymphocytic responses (461,462,463,464 and 465). During pregnancy, the immune response to viruses, such as CMV and rubella,

appears to be depressed (466,467). Finally, certain viral diseases (e.g., influenza, varicella, poliomyelitis, and coxsackievirus) have been associated with increased morbidity and mortality during pregnancy (468). To date, whether pregnancy enhances HIV disease progression remains unclear. Initial reports by Scott et al. (152) and Minkoff et al. (153) suggested that such enhanced progression does occur. These reports noted that 45% to 75% of asymptomatic pregnant women followed for 28 to 30 months after delivery developed AIDS-related complex or AIDS. These rates are higher than the rates of progression reported for asymptomatic HIV antibody-positive homosexual men, IDUs, or hemophiliacs, in whom only 13% to 34% of those followed for up to 6 years developed AIDS (469,470). However, these studies were not controlled and evaluated only pregnant women known to have transmitted HIV to their offspring (152,153). Thus, they may represent a group with a longer duration of HIV infection and/or altered immune function whose progression to symptomatic disease was coincidental to, but not the result of, pregnancy.

More recent controlled studies involving pregnant and nonpregnant asymptomatic HIV-infected women failed to demonstrate that pregnancy accelerates the progressive course of HIV infection (471,472,473,474,475,476,477 and 478). Of some concern was the report by Biggar et al. (479), who assessed immunologic changes over the course of pregnancy and postpartum in 37 HIV-infected and 63 HIV-negative women. Among HIV-negative women, levels of $CD4^+$ counts fell during pregnancy to reach a nadir 8 weeks before delivery, but rose again rapidly before delivery and remained normal postpartum. Among HIV-infected women, a decrease in the number of $CD4^+$ cells was seen through pregnancy, and no postpartum recovery occurred. The $CD8^+$ cell levels were consistently higher in HIV-infected compared to HIV-negative pregnant women. In addition, Biggar et al. (479) noted that the rate of loss of $CD4^+$ cells was 2% per month in pregnant HIV-positive women compared to average rates of 0.5% to 1.0% per month in HIV-infected homosexual men or hemophiliacs. Burns and coworkers (480) assessed T-lymphocyte populations in 192 HIV-infected women compared with 148 non–HIV-infected controls who were followed for 2 years after delivery. They noted that the percentage of CD4 T cells began to increase during pregnancy and returned to normal postpartum. In the HIV-negative control group, the percentage of CD4 cells increased between the third trimester and 12 months postpartum. In contradistinction, in HIV-infected women, CD4 T-cell levels declined steadily during pregnancy and postpartum. However, the clinical significance of these laboratory findings is unclear. Moreover, in the Swiss HIV Cohort Studies, Wiesser et al. (481) noted that when taking into account preconception CD4 cell counts, acceleration of HIV disease progression is consistent in HIV-infected women who became pregnant. The consensus is that pregnancy does not have a major adverse effect on HIV progression (482,483).

HIV Infection and Pregnancy Outcome

Whether HIV infection is associated with an increased risk for adverse pregnancy outcome has been the focus of considerable attention. Initial but retrospective and uncontrolled investigations of infants with AIDS suggested that HIV-infected newborns were at high risk for preterm birth and/or low birthweight (484,485,486 and 487). However, prospective and controlled studies (especially controlled for IDU) in industrialized nations have demonstrated that pregnancy outcome does not appear to be adversely affected by HIV infection (160,161,476,488,489). In general, these studies found no differences in preterm delivery, low birthweight, or

small-for-gestational-age rates between seropositive and seronegative IDUs. Selwyn et al. (476) reported no difference in birth outcomes in HIV-seropositive and seronegative intravenous drug users (Table 10.18). In addition, Selwyn and coworkers (476) reported no differences in the rates of spontaneous or elective abortion, ectopic pregnancy, premature rupture of the membranes (PROM), preeclampsia, anemia, weight gain less than 10 pounds, oligohydramnios, chorioamnionitis, or intrapartum fetal distress. However, seropositive women were significantly more likely to be hospitalized for bacterial pneumonia during pregnancy and had an unexplained increased tendency for breech presentation. Similarly, Johnstone et al. (488) in Scotland reported no significant difference in frequency of preterm birth, low birthweight, PROM, or low Apgar scores for asymptomatic HIV-infected and uninfected women when race, socioeconomic status, and intravenous drug use were controlled for. Minkoff et al. (490) also studied pregnancy outcome in asymptomatic HIV-infected women. In this prospective analysis, 91 HIV-infected and 126 HIV-negative pregnant women were controlled for drug, alcohol, and tobacco use. The HIV-infected women had a significantly higher rate of STDs (17.6% vs. 7.1%) and medical complications of pregnancy (43% vs. 25%), but serostatus was not related to any adverse outcomes, including peripartum fever, preterm labor, PROM, placenta previa, or abruptio placenta (490). In newborns, serostatus was not related to any immediate adverse outcomes, such as gestational age, birthweight, length, head circumference, or Apgar scores (490).

	HIV Seropositive (n = 25)		HIV Seronegative (n = 44)	
Gestational age	≤37 wk	>37 wk	≤37 wk	>37 wk
No. (%)	8 (32%)	17 (68%)	14 (32%)	30 (68%)
Mean birthweight (g)	2,263	3,010	2,390	3,000
Overall mean birthweight (g)	2,760		2,720	
Small for gestational age	3 (12%)		5 (11%)	
Apgar score <7	4 (16%)		6 (13%)	
Any neonatal complication	6 (24%)		14 (31%)	

HIV, human immunodeficiency virus.
Based on Selwyn PA, Schoenbaum EE, Davenny K, et al. Prospective studies of human immunodeficiency virus infection and pregnancy outcomes in intravenous drug users. JAMA 1989;261:1289–1294.

TABLE 10.18. BIRTH OUTCOMES IN HUMAN IMMUNODEFICIENCY VIRUS SEROPOSITIVE AND SERONEGATIVE INTRANVEOUS DRUG USERS

In contrast to the studies from the United States and Europe, prospective studies from Africa comparing pregnancy outcome in HIV-infected and noninfected women suggest that HIV infection adversely affects pregnancy outcome (165,166,491,492,493 and 494). Ryder et al. (166) studied 606 HIV-negative and 406 HIV-infected pregnant women from Kinshasa, Zaire. Acquired immunodeficiency syndrome was present in 18% of the HIV-infected women. These authors reported that rates of preterm birth, low birthweight, low head circumference-to-height ratio, and chorioamnionitis all were higher among infants of symptomatic seropositive mothers with AIDS ($p < 0.01$) than among infants of asymptomatic HIV-infected mothers or seronegative mothers (166). In a study of 177 HIV-infected and 326 uninfected women in Nairobi, Kenya, Braddick and colleagues (491) demonstrated

that women with symptomatic HIV infection were more likely than asymptomatic HIV-infected women or uninfected women to deliver infants of low birthweight (17% vs. 6% vs. 3%). In this study, 17% of patients had advanced HIV disease, 28% had lymphadenopathy, and 55% were asymptomatic (491). In a study comparing 109 HIV-infected women with 40 uninfected women, Hira et al. (165) reported that HIV-infected women were 2.9 times more likely to deliver low birthweight infants. In this study, 50% of the HIV-infected women had symptomatic disease. In a study from Nairobi, Kenya, Temmerman and colleagues (492) controlled for the presence of STDs and reported that HIV-1 infection was significantly and independently associated with prematurity, low birthweight, and stillbirth.

In an update of their study, Temmerman et al. (493) reported on 406 HIV-1 seropositive and 407 HIV-1 seronegative age-matched and parity-matched pregnant women. Maternal HIV-1 infection was associated with significantly lower birthweight (2,913 vs. 3,072 g; $p = 0.0003$) and with prematurity (21.2% vs. 9.4%; $p < 0.0001$), but not with small for gestational age (SGA) (4.2% vs. 3.2%; $p = 0.7$). The stillbirth rate was increased but was not statistically significant (3.8% vs. 1.9%) Women whose $CD4^+$ cell count was less than 30% had a higher risk of preterm delivery (26.3% vs. 10.1%; $p < 0.001$). In addition, postpartum endometritis was more common in HIV-1 infected women than in seronegative controls (10.3% vs. 4.2%; $p = 0.01$) and was inversely correlated with CD4 percentage (493). In a prospective cohort of 318 HIV-infected and 309 seronegative women from Rwanda, Bulterys et al. (494) noted that birthweight was significantly reduced in infants born to HIV-infected mothers. Crown-to-heel length, head circumference, and placental weight also were reduced. These authors reported that maternal HIV infection was significantly associated with intrauterine growth retardation but not preterm birth (494).

The association of HIV infection and low birthweight and preterm birth demonstrated in these African studies probably is related to the advanced maternal HIV infection status noted in these studies. In the United States, pregnancy outcome is similarly adversely affected in symptomatic HIV-infected women (495). Minkoff et al. (495) noted an increased incidence of serious infections in 9 (45%) of 20 HIV-infected pregnant women with CD4 counts less than $300/mm^3$, whereas seronegative or HIV-infected women with CD4 counts greater than $300/mm^3$ had no serious infections. The most common serious infection was PCP, which occurred in six cases. It appears that the more advanced the maternal HIV disease, the greater the likelihood of adverse pregnancy outcomes. Also of concern is the consistent finding that infectious complications, including development of opportunistic infections, are increased in women with more advanced HIV disease (496,497).

Two studies from more developed countries demonstrated that HIV infection was associated with reduced birthweight (498,499). In an analysis of the New York State Medicaid Program, Markson et al. (500) noted that HIV-infected women delivered low birthweight infants more than three times as frequently (29%) as the general sample of Medicaid-enrolled women. However, the authors did not have data related to maternal CD4 T lymphocyte counts and, thus, could not assess the role of HIV disease severity on their findings. Johnstone et al. (499) reported that, after multivariate analysis of their data, HIV had a statistically significant but modest effect on fetal growth, but not on preterm birth. This effect seemed to be associated with placental size, but the small reduction in birthweight seen was less than that

attributable to smoking, and the authors questioned its clinical significance (499).

Risk of Perinatal Transmission of HIV

Vertical transmission of virus from HIV-infected mothers to their infants is a well-established phenomenon that has been a major concern (152,153,160,161,272,404,405,406,407,408,409,410,411,412,413,414 and 415,459,484,486,489,500,501,502 and 503). However, the timing of perinatal transmission, the rate of such transmission, and the determinants of vertical transmission of HIV required further elucidation. HIV transmission from infected mother to infant can occur antepartum *(in utero)*, intrapartum (during labor and delivery), or postpartum (breast-feeding) (272).

Transplacental infection early in pregnancy initially was suggested by description of the AIDS embryopathy syndrome with characteristic facial malformations by Marion et al. (406). However, studies controlling for drug abuse have failed to identify or confirm that such an embryopathy syndrome exists. Subsequent investigations have demonstrated that *in utero* transmission does occur, although it accounts for less than 25% to 30% of perinatal transmission (272). Several different approaches have produced data supporting intrauterine transmission of HIV from mother to fetus. Culture of HIV and identification of HIV via molecular techniques have been reported (404,410,411 and 412,504,505 and 506). In addition, HIV has been identified in amniotic fluid and cells (507). Third, the detection of HIV in blood from newborns at birth has confirmed the presence of *in utero* transmission by culture (414,500,501,504,508,509 and 510), PCR (413,504,508), or p24 antigen with immune-complex dissociation (511).

Infection intrapartum during labor and delivery secondary to ingestion or exposure to blood and other body fluids infected with HIV (i.e., amniotic fluid, cervical secretions) has gained favor as the major route for vertical transmission of HIV. The virus may enter via fetal skin, mucous membranes, or gastrointestinal tract. A number of studies have supported the concept of intrapartum transmission from mother to infant. The data suggest that, in industrialized countries, 70% to 75% of vertical transmission occurs intrapartum (272). Goedert et al. (512) reported the findings of the International Registry of HIV-exposed twins and demonstrated that the first-born twin had a greater risk of HIV infection. Among discordant twins, 25% of first-born twins were HIV infected compared to 8% of second-born twins (512). However, this study did not assess the status of membranes or differentiate elective from emergency cesarean section. On the other hand, in the Italian national study, concordance was present in 18 to 19 twin pairs (513). Ehrnst and colleagues (514) reported that, in a group of HIV-infected women delivering at term, 23 (85%) of 27 women had a positive virus culture (PBMC or plasma). Whereas none of the 27 infants had positive cultures in the newborn period, 5 (26%) of 19 infants had positive cultures by 6 months of age. This study strongly suggests a major role for intrapartum transmission. Rogers et al. (515) noted that detection of HIV-1 by culture, PCR, or p24 antigen methods occurs in 30% to 50% of newborn peripheral blood from infants ultimately shown to be HIV-1 infected. The failure to identify virus in the remaining 50% to 70% supports the concept of intrapartum transmission. Further support is the description by Blanche et al. (516) of a bimodal distribution for development of HIV-1 symptomatic infection in children that may differentiate children infected *in utero* from those who acquire HIV intrapartum. These authors suggest that the children who, by 12 months of age, have advanced HIV-1 infection

with a 26% incidence of AIDS and a 17% mortality were infected *in utero* (515,516). Bryson et al. (409) have proposed a classification system for *in utero* versus intrapartum transmission of HIV. Early *(in utero)* infection requires detection of HIV-1 genome by PCR or isolation of HIV-1 from the blood within 48 hours of birth. Late (intrapartum) infection occurs when HIV isolation, PCR, or serum p24 antigen are negative during the first week of life but become positive from 7 to 90 days after birth in an infant who was not breast-fed.

Dunn et al. (517) performed a meta-analysis of studies that evaluated the use of HIV-1 DNA PCR for early diagnosis of HIV infection. Within 24 hours of birth, HIV infection was detected in 38% (90% CI, 29%–46%), whereas by 28 days HIV was detected in 100% of 271 HIV-infected children. Thus, about 60% of transmission was intrapartum (517). Using serologic testing, DeRossi and coworkers (518) reported that the timing and pattern of antibody to HIV-1–specific proteins (develop at mean 54 days in 70% infected infants) also was consistent with intrapartum transmission and the time to seroconversion following acute infection with HIV in adults. Rouzioux et al. (519) reported similar estimates using mathematical modeling to estimate the timing of vertical transmission in a non–breast-feeding group. These authors estimated that 65% (95% CI, 22%–92%) of perinatal transmission occurred intrapartum. Moreover, the model suggested that 92% of all transmission occurred during the last 2 months before or during the intrapartum period (519). More recently, Bertolli and coworkers (186), using virologic detection in a breast-feeding population, reported that the proportion of transmission estimated to occur *in utero* was 26% (95% CI, 14%–35%), intrapartum/early postpartum was 65% (95% CI, 53%–76%), and late postpartum via breast-feeding was 12% (95% CI, 5%–20%). Similarly, Kalish and coworkers (520) assessed 140 infected infants in the Women and Infants Transmission Study (WITS) and reported that HIV-1 culture was positive in 27% at 48 hours (*in utero* transmission), with transmission usually occurring during the intrapartum period. Clearly, the twin study with the first-born twin having twice the risk for acquiring HIV infection suggests that exposure to infectious secretions of the cervix and/or vagina plays a critical role in the intrapartum transmission of HIV from mother to infant (512). Subsequently, Duliege et al. (521) estimated that greater than 50% of the risk of transmission in first-born twins was the result of vaginal delivery; this increased to 76% when vaginally delivered first-born twins were compared to second-born twins delivered via cesarean section. Additional evidence that exposure to infected genital tract secretions is a substantial risk for perinatal transmission of HIV is provided by studies demonstrating an increased risk of vertical HIV transmission associated with increased duration of rupture of the membranes (ROM) prior to delivery (522,523).

The third possible route for perinatal transmission of HIV is postpartum via breast-feeding. Human immunodeficiency virus has been recovered from the breast milk of infected women (179,524) and is found in the highest concentration in colostrum (525). Transmission of HIV via breast-feeding has been demonstrated (407,524,526). The viral load of HIV is significantly higher from a blood transfusion than with chronic HIV infection (180). Thus, Lederman (180) proposed that women who contracted HIV from a contaminated transfusion while breast-feeding represent a group at greater risk for transmission than mothers who have chronic HIV infection. Similarly, Van de Perre et al. (181) demonstrated that transmission via breast-feeding was associated with acute HIV infection that is characterized by high viral titers. Workers in Australia also documented an association between primary maternal HIV infection and a high risk of transmission via breast milk (182). Thus, the risk of transmission via breast-feeding appears to be very high when maternal

primary infection occurs within the first few months after delivery (182). Studies from Europe have provided epidemiologic data (marginally statistically significant) supporting an association between breast-feeding and increased risk of HIV transmission (171,527). In Africa, the higher vertical transmission rates reported to some degree may be attributable to a high rate of breast-feeding (165,166). However, in a prospective study from Zaire, Ryder et al. (528) could not demonstrate a dose-response effect between breast-feeding and perinatal HIV transmission. Moreover, they confirmed a protective effect of breast-feeding against other common causes of childhood morbidity and mortality. Datta et al. (529) noted that the risk of transmission via breast-feeding was 32% if an infected mother breast-fed her infant for more than 15 months. Dunn and coworkers (524) performed a meta-analysis and reported that the attributable risk of transmission via breast-feeding was an estimated 29% (95% CI, 16%–42%) if the mother became infected postpartum compared to 14% (95% CI, 7%–22%) if the mother was infected before pregnancy. In industrialized countries, it is recommended that HIV-infected women not breast-fed (530). On the other hand, in developing countries, the benefits of breast-feeding definitely outweigh the risk of HIV transmission via breast-feeding. In July 1998, the World Health Organization recommended that HIV-infected women in developing countries be informed regarding the benefits and risks of breast-feeding and be given an opportunity to make an informed choice about breast-feeding (531).

To maximize prevention of perinatal AIDS, HIV-infected women must be identified as early as possible in pregnancy (272). Similarly, postdelivery evaluation of the infant at risk for HIV infection immediately after birth is crucial for early diagnosis and optimal medical treatment (272). Serologic methods have limited usefulness for the early diagnosis of perinatal HIV infection due to transplacental passage of maternal immunoglobulin G antibodies that may last up to 18 months (272). Detection of HIV proviral genome using PCR (DNA PCR) or HIV RNA using PCR is a highly sensitive, specific, rapid, and cost-effective screening test for vertical infection (532,533). Using DNA PCR, 25% to 30% of HIV-infected infants may be identified at birth, with the remaining 70% to 75% of HIV-infected infants diagnosed by 1 month of age (272).

Mother-infant (vertical) transmission of HIV has been both a concern and a focus of intense research efforts. In the United States, vertical transmission of HIV accounts for virtually all new HIV infections in children (4). Initial studies demonstrated vertical transmission rates as high as 65% (152,153 and 154). However, these initial estimates of the risk for perinatal transmission were based on studies assessing subsequent infants born to mothers who previously had given birth to an HIV-infected child or mothers with advanced HIV disease (152,153 and 154). In retrospect, this most likely represented a subgroup of women with advanced HIV disease, high viral loads, and low CD4 T-lymphocyte counts. Subsequent prospective studies that followed HIV-seropositive pregnant women and their infants revealed lower estimates of transmission, with interesting differences in vertical transmission rates noted worldwide (534). Prior to widespread use of antiretroviral therapy, vertical transmission rates in the United States and western Europe ranged from 14% to 33%; in Africa, rates ranged from 20% to 45%; and in India, a rate of 48% has been reported (Table 10.19). Mofenson (534) suggested that these observed geographic variations in transmission rates may be due to several factors, including (i) duration and severity of maternal HIV infection; (ii) genotypic and phenotypic viral variants present in various geographic areas; (iii) differences in the incidence of cofactors (e.g., STDs, chorioamnionitis); and (iv) differences in infant

feeding practices.

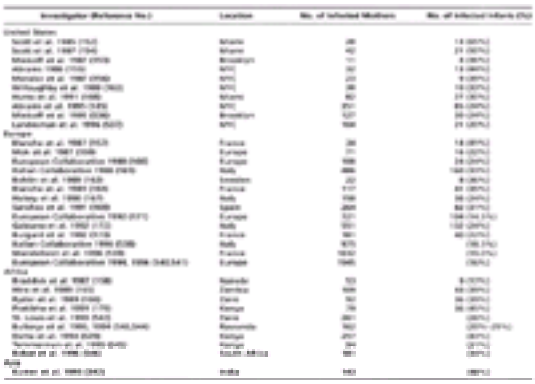


TABLE 10.19. REPORTED RATES OF PERINATAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS

As noted by the Institute of Medicine, the variable transmission rates reported reflects the multiple factors that influence perinatal transmission (272). This is not surprising, given that studies prior to widespread availability of antiretroviral therapy demonstrate that mother-infant transmission can be influenced by a variety of maternal biologic factors. Most recent interest has focused on the role of maternal viral load in determining perinatal transmission of HIV. Studies have linked high maternal viral load to increased risk of HIV perinatal transmission (548,549,550,551,552,553,554,555,556,557,558,559,560 and 561). Contopoulos-Ioannidis and Ioannidis (558) performed a meta-analysis of the predictive value of maternal cell-free viral load in vertical transmission of HIV-1 in 696 untreated and 419 treated mother-infant pairs. The pooled rate of transmission in untreated women in the <1,000, 1,000 to 9,999, and ³10,000 copies/mL categories were 5% (95% CI, 2%–11%), 15% (95% CI, 11%–20%), and 37% (95% CI, 29%–46%), respectively. Transmission rates for treated women for these groups were 5% (95% CI, 2%–11%), 7% (95% CI, 4%–11%), and 18% (95% CI, 12%–27%) respectively, reflecting an attenuation of the risk gradient in treatment women (558). Use of p24 antigen level as a marker for viral load also has demonstrated that p24 antigenemia is associated with increased mother-child transmission of HIV (562,563). Although these studies demonstrate that the level of plasma HIV-1 RNA predicts the risk of vertical transmission, no absolute viral threshold value that can discriminate between transmitters and nontransmitters has been identified; transmission has been observed across the full range of viral levels (272). Thus, although maternal viral load is an important predictor of perinatal transmission, other factors also contribute to the risk of transmission (564).

Maternal Factors

Other determinants of perinatal HIV transmission can be divided into maternal, obstetric, infant, and viral factors (176). Maternal factors include (i) advanced maternal HIV disease (171,165,565,566); (ii) decreased $CD4^+$ T lymphocytes or percentage (171,172,542,566,567,568,569 and 570); (iii) injection drug use

(171,571); (iv) decreased maternal vitamin A levels during pregnancy (vitamin A stimulates the immune system and helps maintain the integrity of mucosal surfaces) (572,573); and (v) presence of STDs (372,373). The Consensus Workshop on maternal factors involved in mother-child transmission of HIV-1 suggested that the level and specificity of maternal HIV-specific antibody may influence vertical transmission of HIV (575). The finding that increased transmission of HIV occurs with premature delivery (171,568,575) and that the vast majority of mother-child transfer of antibody occurs after 32 weeks' gestation has been cited as evidence that maternal antibody may play a role (534).

Several initial studies that produced tremendous interest and excitement suggested that HIV-1–infected pregnant women with high antibody titers to certain epitopes of the V3 loop of the gp120 envelope protein had a lower rate of vertical transmission (568,576,577). However, subsequent investigations failed to confirm this finding (578,579 and 580). Several small studies of mother-infant pairs demonstrated that transmitting mothers had antibody to their own virus less frequently than those who did not transmit HIV to their infants (581,582). Interestingly, transmitting mothers rarely had neutralizing antibody to the viral isolate from their infant. On the other hand, the role of the maternal cell-mediated immune response to HIV, represented by maternal HIV-1–specific antibody-dependent cellular cytotoxicity, has not been demonstrated to protect against transmission (583,584). However, in HIV-infected children, it does correlate with less severe clinical disease (584).

Fetal and Infant Factors

Mofenson (534) reviewed the fetal and infant determinants of vertical HIV transmission. Among the fetal factors are (i) increased fetal cell susceptibility to HIV infection (e.g., thymic cells, neonatal/cord blood macrophages) (585,586); (ii) reduced functional immune competence; and (iii) genetic susceptibility associated with certain human leukocyte antigen haplotypes (587,588). Newborn factors include skin integrity, low gastric acid secretion, and decreased functional immune responsiveness (176,534). A variety of factors related to breast-feeding have been suggested, including cell-associated viral load, cell-free viral load, higher viral load in colostrum, and HIV-specific antibody (176,534). Van de Perre (589) demonstrated that maternal immune status and the detection of HIV in breast milk by PCR were the most predictive factors for transmission of HIV via breast-feeding.

Obstetric Factors

Invasive obstetric procedures have been associated with an increased risk of mother-infant transmission of HIV (176,534). Limited data are available on antepartum testing (e.g., amniocentesis, chorionic villus sampling, and fetal blood sampling) relative to the risk of HIV transmission (590). In a report from the French perinatal cohort, Mandelbrot et al. (562) noted a twofold increase in transmission with such antenatal procedures.

Whereas the initial report from the European Collaborative Study (171) demonstrated an association between episiotomy and vertical transmission of HIV, this was no longer the case with additional enrollment of mother-infant pairs (541). Moreover, additional studies have shown no significant association between

episiotomy and vertical transmission (537,562,581).

It has been suggested that use of fetal scalp electrodes increases fetal exposure to maternal blood and genital tract secretions, which in turn increases the risk of vertical transmission (590). In their initial report, the European Collaborative Study noted an increased ransmission rate with use of fetal scalp electrodes (171). However, subsequent larger studies did not confirm this finding (537,541,562). Similarly, operative vaginal deliveries (e.g., forceps, vacuum) were associated with an increased risk of transmission initially (171), but this finding was not confirmed in subsequent studies (562).

Several early epidemiologic studies suggested that the vertical transmission rate is lower for cesarean section compared to vaginal delivery (168,171,172,512,527). However, considerable controversy existed as to the validity of this association; thus, there was no consensus on recommendations for the optimal route for delivery of HIV-infected pregnant women. Villari et al. (591) performed a meta-analysis in which they reported a 14% transmission in the cesarean delivery group compared to 20% in women delivered vaginally. Pooling the data from all studies meeting their eligibility criteria, Villari and coworkers demonstrated a statistically significant difference of HIV perinatal transmission rates between cesarean and vaginal delivery (OR, 0.65; 95% CI, 0.43–0.99; $p = 0.044$). However, as noted by these authors, about 16 HIV-infected women must deliver by cesarian section in order to prevent one case of HIV perinatal infection. Studies performed prior to routine viral load assessment and antiretroviral therapy demonstrated that cesarean delivery performed before the onset of labor and ROM (elective cesarean) was associated with a significant decrease in perinatal HIV-1 transmission compared to other types of delivery, with reductions ranging from 55% to 80% (592). A summary of the data on transmission rates stratified by receipt or no receipt of ZDV is given in Table 10.20. In the meta-analysis, which included more than 7,800 mother-child pairs accrued from 15 prospective studies, the rate of perinatal HIV-1 transmission in women who underwent elective cesarean delivery was significantly decreased compared to women who underwent nonelective cesarean section or who delivered vaginally, whether or not they received ZDV (593). In the European Mode of Delivery Collaboration, a prospective randomized study of delivery mode, perinatal HIV transmission was 1.8% in the entire group (many who received ZDV) randomized to elective cesarean (4% in no ZDV group vs. 1% ZDV group) (594). Interestingly, although the magnitude of the reduction in perinatal transmission associated with elective cesarean compared to vaginal delivery in women receiving ZDV was similar to that in untreated women, this was not statistically significant (594). In addition, in both studies, nonelective cesarean delivery was not associated with a significant decrease in perinatal transmission of HIV compared to vaginal delivery (593,594). As a result of these studies, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice issued a Committee Opinion relative to the route of delivery in HIV-infected pregnant women (595).

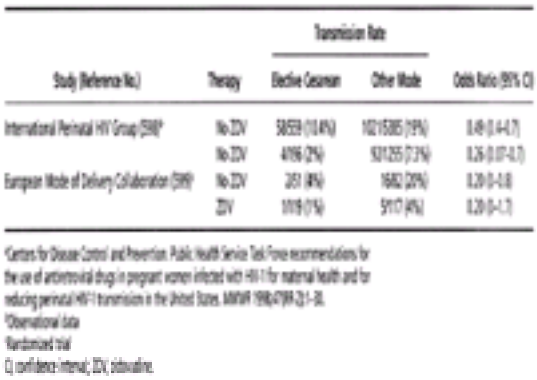


TABLE 10.20. RATE OF PERINATAL TRANSMISSION ACCORDING TO RECEIPT OF ZIDOVUDINE DURING PREGNANCY AND MODE OF DELIVERY[a]

It is important to balance this enthusiasm for elective cesarean delivery by the increased maternal morbidity and mortality associated with cesarean delivery compared to vaginal delivery in women not infected with HIV. Postpartum infections are five to seven times more common with nonelective cesarean delivery than vaginal delivery, and complications after elective cesarean delivery are intermediate between those associated with vaginal delivery and nonelective cesarean delivery (596,597,598,599,600,601 and 602). Complications of cesarean delivery appear to be similar in HIV-infected women as those seen in non–HIV-infected women (592). Among HIV-infected women undergoing cesarean delivery, postpartum fever and/or infections were more common than among HIV-infected women delivered vaginally (594,603,604,605,606,607 and 608). Of concern is the report by Bulterys et al. (544) from Rwanda demonstrating an increased frequency of maternal deaths following cesarean delivery in HIV-infected versus uninfected women.

An association of increasing duration of ROM and risk for perinatal transmission of HIV in predominantly untreated HIV-infected women has been demonstrated (536,537,609). Minkoff et al. (536) reported that delivery more than 4 hours after ROM was associated with a nearly twofold increased rate of perinatal transmission in women delivered vaginally and in those whose $CD4^+$ T-lymphocyte counts were low, regardless of the route of delivery. Similarly, Landesman et al. (537) noted a near twofold increased risk of transmission with ROM more than 4 hours, controlled for other risk factors of transmission. The findings have ben inconsistent in women treated with ZDV; same studies have shown that the risks of transmission increases with longer duration of ROM (559,610), whereas others have not (611,612).

Factors associated with placental disruption have been associated with an increased risk of perinatal transmission of HIV (176). As a consequence of disruption in the placental barrier, mixing of maternal and fetal cells and/or blood could occur (176). Prominent among these factors is chorioamnionitis, which has been demonstrated in several investigations to be associated with an increased risk of mother-child transmission of HIV (166,532,575). St. Louis et al. demonstrated in a multivariate analysis that placental membrane inflammation was an independent risk factor for perinatal transmission of HIV (OR, 2.5; 95% CI, 1.2–5.2) (580). Other conditions associated with placental disruption and increased risk of transmission include

cigarette smoking (613) and illicit drug use (571).

Antiretroviral Therapy and Prevention of Vertical Transmission

Use of antiretroviral therapy in pregnant HIV-infected women has been shown to significantly decrease the risk for perinatal HIV transmission (592). In February 1994, Connor et al. (452) reported the results from PACTG 076 demonstrating that a three-part (antepartum, intrapartum, and neonatal) regimen of ZDV (Table 10.21) reduced the risk of mother-infant transmission of HIV by nearly 70% in a group of minimally symptomatic pregnant HIV-infected women; reduction from a transmission rate 25.5% (95% CI, 18.4%–32.5%) in the placebo group to a rate of 8.3% (95% CI, 3.9%–12.8%) occurred (452). Subsequent to publication of the results of PACTG 076, additional epidemiologic studies in the United States and France confirmed the dramatic decrease in perinatal transmission of HIV associated with use of the PACTG 076 ZDV regimen (610,613,614,615,616 and 617).

Time of ZDV Administration	Regimen
Antepartum	Oral administration of 100 mg Zidovudine (ZDV) five times daily, initiated at 14–34 wks' gestation and continued throughout the pregnancy
Intrapartum	During labor, intravenous administration of ZDV in a 1-hr initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight until delivery
Postpartum	Oral administration of ZDV to the newborn ZDV syrup at 2 mg/kg/dose every 6 hr for the first 6 wk of life, beginning at 8–12 hours after birth

TABLE 10.21. PEDIATRIC AIDS CLINICAL TRIAL GROUP (PACTG) 076 ZIDOVUDINE REGIMEN

In 1996, Sperling et al. (453) reported the final results of 419 infants enrolled in PACTG 076. The HIV transmission rate was 22.6% in the placebo group and 7.6% in the ZDV-treated group, a two-thirds reduction. Subsequent studies assessed the efficacy of ZDV chemoprophylaxis for decreasing perinatal transmission of HIV in pregnant women with more advanced HIV disease against those enrolled in PACTG 076. Stiehm et al. (618) reported the results from PACTG 185, in which pregnant women with advanced HIV disease, low $CD4^+$ T-lymphocyte counts, and previous antiretroviral therapy and their newborns received the three-part ZDV regimen. The combined group transmission rate was 4.8%. Additional studies documented rates of mother-child transmission as low as 3% to 4% in HIV-infected women who received all three components of the ZDV regimen, including women with advanced disease (615,618).

Several clinical trials from developing countries have assessed the efficacy of short-course antiretroviral prophylaxis for prevention of perinatal HIV transmission (619,620,621,622 and 623). In non–breast-feeding women in Thailand, a

short-course antepartum/intrapartum ZDV regimen (ZDV 200 mg twice a day for 4 weeks antenatally and 300 mg every 3 hours orally during labor) reduced perinatal transmission by approximately 50% compared to placebo (from 19% to 9%) (619). The PETRA trial in Africa, which enrolled breast-feeding HIV-infected women, reported that a combination regimen of ZDV and lamivudine (3TC) administered to the woman and infant starting at 36 weeks' gestation, orally intrapartum, and for 1 week postpartum reduced transmission from 17% in the placebo group to 9% in the three-part ZDV/3TC regimen (620). Short-course intrapartum/postpartum antiretroviral regimens also have been evaluated as an intervention for women not diagnosed with HIV infection until they were near to, or in, labor. The PETRA study of breast-feeding African women demonstrated that ZDV/3TC started during labor and continued for 1 week postpartum to mother and infant reduced transmission of HIV at 6 weeks' of age from 17% in the placebo group to 11% (38% reduction) in the ZDV/3TC group (620). Oral ZDV/3TC administered only intrapartum was not effective in reducing perinatal transmission (620). Guay et al. (621) reported in a study from Uganda that in breast-feeding women, a single 200-mg oral dose of nevirapine (a nonnucleoside RT inhibitor [NNRTI]) given at the onset of labor, combined with a single 2 mg/kg oral dose given to the infant at 48 to 72 hours of age, reduced perinatal HIV transmission by nearly 50% compared to a short regimen of ZDV given orally during labor and to the infant for 1 week (12% vs. 21% at age 6 weeks). Postpartum antiretroviral prophylaxis alone has produced inconsistent results. Fiscus et al. (615), in a study from North Carolina, noted that the rate of perinatal transmission was not reduced in HIV-exposed infants who received only postpartum ZDV prophylaxis. On the other hand, studies from New York State reported that ZDV initiated within 24 hours of birth and given to the infant for 6 weeks significantly reduced transmission of HIV (622,623).

There has been substantial progress since 1994 related to our understanding of the pathogenesis of HIV-1 infection and the treatment and monitoring of HIV-1 disease (592). As a result, antiretroviral monotherapy is now considered suboptimal for treatment, and combination therapy is the current standard of care (592,624). The current therapeutic approach emphasizes early initiation of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce development of viral resistance (625). Currently, combination antiretroviral therapy (generally two nucleoside analogue RT inhibitors and a protease inhibitor) is the recommended standard treatment for HIV-1–infected adults who are not pregnant (624). The PHS Task Force recommends that pregnancy should not preclude the use of optimal therapeutic regimens (592). However, limited data have been reported on the use of combination antiretroviral therapy in pregnancy (592). Thus, as reviewed by the PHS Task Force, whether lowering maternal HIV-RNA copy number during pregnancy would reduce the risk of perinatal transmission of HIV has not yet been determined (592). Melvin et al. (626) studied 44 HIV-1–infected pregnant women and noted that ZDV was effective in reducing transmission even though minimal effect was demonstrated on HIV-1 RNA levels. Two reports documented that pregnant women receiving HAART, which effectively reduces viral load, have very low rates of perinatal transmission (627,628). Several studies have reported that women with low or undetectable HIV-1 RNA levels (e.g., <1,000 copies/mL) have extremely low rates of perinatal transmission (559,611,627). Similarly, low mother-child HIV transmission rates have been demonstrated in the limited group of women who have received combination antiretroviral therapy during pregnancy. Studies reported to date have noted transmission in 1 (6.7%) of 15, 0 of 30, and 0 of 24 (1/69 [1.5%]) women receiving two or more antiretroviral drugs in combination during pregnancy (628,629 and 630). Preliminary reports presented as

abstracts also have demonstrated very low rates of transmission: 0 of 153 women receiving combination HAART (627) and 2 (1%) of 187 (631) and 3 (5.8%) of 52 women receiving triple therapy, including a protease inhibitor (631,632).

Risk Factors for Perinatal HIV Transmission With Antiretroviral Therapy

The described studies assessing risk factors were conducted primarily before the widespread use of ZDV and now HAART for prevention of perinatal transmission. Several published studies now have addressed the issue of risk factors for perinatal transmission among HIV-1–infected women and infants who received ZDV (551,552,559,610,611 and 612,633). Mofenson et al. (611), in mother-infant pairs enrolled in ACTG study 185, examined the effects of maternal-, obstetric-, and infant-related characteristics and maternal virologic and immunologic variables on the risk of perinatal transmission of HIV in 480 women and their infants, all of whom received ZDV. In their univariate analysis, the risk of perinatal transmission was associated with decreased maternal $CD4^+$ lymphocyte counts at baseline; decreased maternal HIV-1 p24 antibody level at baseline and delivery; increased maternal HIV-1 titer at baseline and delivery; increased maternal HIV-1 RNA levels at baseline and delivery, and the presence of chorioamnionitis at delivery. With multivariate analysis, the only independent risk factor remaining was maternal HIV-1 RNA level at baseline (OR for transmission, 2.4 per log increase in the number of viral copies; 95% CI, 1.2–4.7) and at delivery (OR, 3.4; 95% CI, 1.7–6.8). Chorioamnionitis was associated with a nonsignificant trend (OR, 4.4; 95% CI, 1.0–20.6; $p = 0.06$). However, histologic data were not collected, and the diagnosis of chorioamnionitis was based on a clinical diagnosis; thus, the prevalence of chorioamnionitis was low (4%), which limited the study's ability to detect a significant trend (611). No perinatal transmission of HIV-1 occurred among the 84 women who had HIV-1 levels below the limit of detection (500 copies/mL) at baseline or the 107 women with undetectable levels at delivery (611). Similarly, Garcia et al. (559), reporting from the Women and Infants Transmission Study (WITS) Group, demonstrated that the level of plasma HIV-1 RNA predicts the risk of HIV transmission. These authors noted that increasing geometric mean levels of plasma HIV-1 RNA were associated with increasing rates of transmission: 0% (0/57) in women with <1,000 copies/mL, 16.6% (32/193) at 1,000 to 10,000 copies/mL, 21.3% (39/183) at 10,001 to 50,000 copies/mL, 30.9% (17/54) at 50,001 to 100,000 copies/mL, and 40.6% (28/64) at >100,000 copies/mL. In addition, Van Dyke et al. (612), reporting from the Ariel Project, noted with univariate analysis that histologic chorioamnionitis, prolonged ROM, and a history of genital warts were significantly associated with transmission. Other factors associated with transmission that approached significance included a higher maternal viral load at delivery and presence of cocaine in the urine. In their logistic regression model, only histologic chorioamnionitis was retained as an independent predictor of transmission in women receiving ZDV (612).

Management of Pregnant Women Infected with HIV

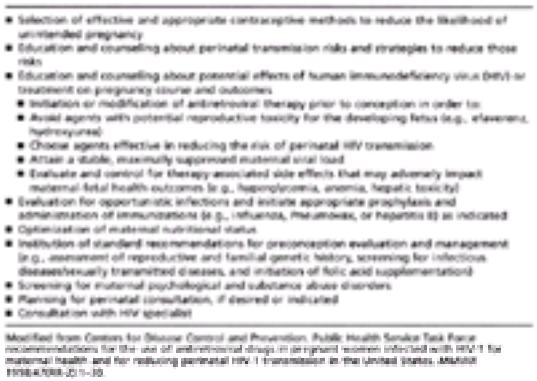
Optimal management of pregnant HIV-infected women requires that obstetric providers identify which women are HIV infected and in seropositive women determine the stage of their HIV disease. Following publication of the dramatic results from the PACTG 076 study (452,453), the PHS Task Force issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the United States (56). The ACOG concurred with those recommendations (634). Providers of obstetric care are in a position to identify

risk factors, offer HIV testing, and provide appropriate education and counseling regarding HIV infection and its prevention. Knowledge of the patients' HIV status allows for an informed decision about prevention, termination, or continuation of pregnancy. Moreover, such knowledge provides the opportunity for decisions regarding the use of antiretroviral drugs during pregnancy (592).

Preconceptional Counseling of HIV-Infected Women

Preconceptional counseling has evolved dramatically over the past 2 decades, resulting in dramatically improved outcomes in pregnancies complicated by a variety of medical illnesses, including diabetes, chronic hypertension, seizure disorders, and autoimmune diseases (634). The PHS Task Force notes that as many as 60% of women infected with HIV enter pregnancy with a known diagnosis, and nearly 50% of these women enter the first trimester of pregnancy taking antiretroviral treatment (single or multiple agent) (592). Tuomala et al. (635) reported that up to 40% of women receiving antiretroviral therapy before pregnancy may require adjustment of their regimen during pregnancy.

The ACOG recommends that all women of childbearing age have the opportunity to receive preconceptional counseling as part of routine primary care (636). For HIV-infected women, preconceptual counseling and care also must address maternal infection status, viral load, immune status, and antiretroviral treatment regimen (592). These women should receive education regarding perinatal transmission risks, strategies for prevention of perinatal transmission, and expectations for the child's future (592). Moreover, counseling and education about effective contraception is crucial (where desired) to delay pregnancy until optimal maternal health status for pregnancy is achieved (592). The components of preconceptional counseling for HIV-infected women recommended by the PHS Task Force are summarized in Table 10.22.



- Selection of effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy
- Education and counseling about perinatal transmission risks and strategies to reduce those risks
- Education and counseling about potential effects of human immunodeficiency virus (HIV) or treatment on pregnancy course and outcomes
  - Initiation or modification of antiretroviral therapy prior to conception in order to:
  - Avoid agents with potential reproductive toxicity for the developing fetus (e.g., efavirenz, hydroxyurea)
  - Choose agents effective in reducing the risk of perinatal HIV transmission
  - Attain a stable, maximally suppressed maternal viral load
  - Evaluate and control for therapy-associated side effects that may adversely impact maternal-fetal health outcomes (e.g., hyperglycemia, anemia, hepatic toxicity)
- Evaluation for opportunistic infections and initiate appropriate prophylaxis and administration of immunizations (e.g., influenza, Pneumovax, or hepatitis B) as indicated
- Optimization of maternal nutritional status
- Institution of standard recommendations for preconception evaluation and management (e.g., assessment of reproductive and familial genetic history, screening for infectious diseases/sexually transmitted diseases, and initiation of folic acid supplementation)
- Screening for maternal psychological and substance abuse disorders
- Planning for perinatal consultation, if desired or indicated
- Consultation with HIV specialist

Modified from Centers for Disease Control and Prevention. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. MMWR 1998;47(RR-2):1–30.

TABLE 10.22. COMPONENTS OF PRECONCEPTIONAL COUNSELING FOR HIV-INFECTED WOMEN RECOMMENDED BY THE PUBLIC HEALTH SERVICE TASK FORCE FOR USE OF ANTIRETROVIRAL DRUGS IN PREGNANT HIV-1 INFECTED WOMEN FOR MATERNAL HEALTH AND INTERVENTIONS TO REDUCE PERINATAL TRANSMISSION IN THE UNITED STATES

The National Institutes of Health has defined the principles of therapy of HIV infection and established guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (364). For treatment of HIV disease in women of reproductive age, they recommend that women receive optimal antiretroviral therapy regardless of pregnancy status. In addition, in women already receiving antiretroviral therapy at the time pregnancy is diagnosed, it is recommended that their therapy be continued. However, if antiretroviral therapy is discontinued for any reason during the first trimester (e.g., fetal toxicity concerns secondary to antiretroviral agents), all agents should be discontinued simultaneously. When they are reinstituted, all drugs should be introduced simultaneously to minimize development of viral resistance. Patients should be informed that interruption of antiretroviral therapy is likely to result in rebound of plasma HIV RNA levels to pretreatment levels or higher (634).

Transient increases in plasma HIV-1 RNA levels have been reported in association with immunizations, suggesting that vaccination may lead to activation of virus replication (637). Therefore, many experts advise that, when possible, all indicated vaccinations should be given before conception rather than during pregnancy (634). In addition, an effort should be made to undertake vaccination when viral replication is under maximal control.

Counseling and Education of HIV-Infected Pregnant Women

Testing for HIV antibody in combination with counseling will allow women to make informed decisions regarding their reproductive health and behavior. For this reason, HIV testing and counseling have been recommended in any medical setting in which women at risk for HIV infection are encountered (51), including clinics offering family planning, prenatal care, gynecologic care, and diagnosis and treatment of STDs. In particular, such testing and counseling should be offered to women in high-risk groups. These risk groups include current or former IDUs and women whose sexual partners are IDUs, are bisexual, or have evidence of HIV infection. Additional risk groups include women with other STDs (especially ulcerative), women who have engaged in prostitution, or women who received blood transfusion or blood products between 1978 and 1985. Finally, women from areas with a high prevalence of heterosexual transmission of HIV (i.e., Haiti, sub-Saharan Africa, southeast Asia) and women who are concerned about or uncertain about the drug use or sexual history of their sexual partner(s) should be counseled and screened. However, up to one half of HIV-infected women do not have a history of or acknowledge the presence of any risk factor. Two factors, the increasing prevalence of HIV-infected women in the reproductive age group and studies demonstrating that antiretroviral therapy of pregnant women significantly decreases the risk of vertical transmission, resulted in recommendations for routine antenatal screening for HIV.

In July 1995, the PHS issued guidelines recommending that all pregnant women receive routine HIV counseling and voluntary testing of HIV serostatus (56). In an assessment of the economic impact of these recommendations, Mauskopf et al. noted that implementing voluntary prenatal testing and treating seropositive women and their newborns was both cost effective and reduced the number of pediatric HIV infection cases (637a). Identification of HIV-infected women early in pregnancy is important not only because it provides an opportunity to provide early administration of antiretroviral therapy to minimize perinatal transmission, but it also allows early treatment of maternal HIV disease to optimize the mother's health and long-term

prognosis (634). Moreover, undiagnosed and treated advanced-stage HIV infection in pregnancy is associated with significant maternal morbidity and mortality, especially when it is associated with serious opportunistic infections (e.g., PCP) (495,634). These guidelines from the PHS recommended pretest counseling, written informed consent, and posttest counseling. As noted by Lindsay and Nesheim (297), HIV-infected pregnant women should receive comprehensive posttest counseling given by an individual who is knowledgeable about the interaction of HIV and pregnancy, including options for antiretroviral therapy. In addition, seropositive women should be counseled that (i) they are not at increased risk for progression of HIV disease due to pregnancy; (ii) there is not an increased risk of adverse pregnancy outcomes unless severe HIV disease is present; and (iii) there is a risk for HIV transmission to the fetus or newborn that can be reduced with antiretroviral treatment during pregnancy.

As suggested by the PHS Task Force, the medical care of HIV-infected pregnant women requires coordination and communication between the HIV specialist caring for women before pregnancy or consulting for women newly diagnosed with HIV infection during preconceptional/prenatal care and the obstetric care provider (592). Pregnant women must make a decision related to use of antiretroviral therapy during pregnancy following discussion about known and unknown benefits and risks of therapy (592). The initial evaluation of HIV-infected pregnant women should include assessment of HIV disease status and recommendations regarding antiretroviral therapy or alteration of the current antiretroviral regimen (592). Such an assessment should include (i) $CD4^+$ lymphocyte count to determine degree of immunodeficiency; (ii) level of plasma HIV-1 RNA to determine the risk of disease progression; (iii) detailed history of prior or current antiretroviral therapy; (iv) establishment of gestational age; and (v) supportive psychosocial care needs (592). The PHS Task Force has stressed that decisions regarding initiation of antiretroviral therapy should be the same for women not currently receiving antiretroviral therapy and for nonpregnant women (592). However, consideration must be given to the potential impact of antiretroviral therapy on the fetus and/or infant (624). In a similar vein, for pregnant women currently receiving antiretroviral agents, alterations in therapeutic regimens should be based on the same guidelines used for nonpregnant women. The PHS Task Force currently recommends that use of the three-part ZDV regimen should be discussed with, and offered to, all HIV-infected women to reduce the risk of mother-infant transmission of HIV (592).

Use and choice of antiretroviral drugs during pregnancy involves a complex set of competing factors that influence the risks and benefits and must be weighed (592). This analysis should include (i) what is known and not known regarding effects of antiretroviral agents on the fetus and newborn, including lack of long-term outcome data on any of the available antiretroviral agents; (ii) what is recommended in terms of treatment for the health of HIV-infected women; and (iii) the efficacy of ZDV in reducing perinatal HIV transmission. It is important to place the theoretical risks of antiretroviral agents in perspective compared to the documented benefit of antiretroviral therapy on the health of infected women and the benefit of ZDV chemoprophylaxis for significantly decreasing the risk of perinatal transmission of HIV (592). These discussions of treatment options should be nonjudgmental and noncoercive, with the final decision regarding use of antiretroviral therapy being the woman's responsibility.

According to the PHS Task Force, general counseling and education should provide

information about what is known about risk factors for perinatal transmission, such as cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners (571,613,637,638,639 and 640), discontinuation of which may result in nonpharmacologic interventions that may reduce the risk for mother-infant HIV transmission (592). In addition, the PHS recommends that HIV-infected women in the United States not breast-feed to prevent neonatal acquisition of HIV (56,640).

Holman et al. (641) and the Working Group on HIV Testing of Pregnant Women and Newborns (642) have published excellent reviews of prenatal counseling and testing for HIV-1. Reproductive options, including elective abortion, should be discussed with HIV-infected women seen early in pregnancy (51,634,643). As stressed by Landers et al. (643), if the physician is unable to provide care to HIV-infected women in a supportive and nonjudgmental way, referral to a qualified individual who can provide such care should be made. Following pregnancy, these women will require specialized and ongoing primary care.

Antepartum Care

In addition to the counseling and education (described earlier) that are critically important to the antepartum care of established or newly recognized HIV-infected pregnant women, HIV-infected pregnant women require thorough clinical evaluation (297,634). Several publications have provided detailed guidelines for the assessment and management of HIV infection in pregnancy (297,634,646,647 and 648). A brief overview of the prenatal management of HIV-infected patients follows. At the initial prenatal assessment, HIV-infected women should undergo a complete history, thorough physical examination, and detailed laboratory assessment (Table 10.23).

Complete history and physical examination
HIV-1 RNA viral level
CD4⁺ lymphocyte count, CD4⁺ percentage
Complete blood count with differential
Platelet count
Screen for sexually transmitted diseases (gonorrhea, chlamydia, syphilis, herpes simplex virus)
Hepatitis serology for B and C
Screen for cytomegalovirus and toxoplasmosis (serology)
Papanicolaou smear
Purified protein derivative (PPD) tuberculosis skin test

TABLE 10.23. ANTEPARTUM ASSESSMENT OF HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PREGNANT WOMEN

It is important to recognize that many of the nonspecific symptoms associated with early pregnancy, such as fatigue, anorexia, and weight loss, also may be early clinical manifestations of HIV infection. Thus, HIV-infected patients should be encouraged to report promptly all such symptoms so they can be appropriately evaluated and defined. In addition, nutritional counseling is important to help

maintain adequate weight gain during pregnancy. All HIV-infected women should be questioned regarding use of injecting drugs and cocaine. These patients require a very thorough physical examination at their initial prenatal visit, paying particular attention to organ systems identified by the individual's symptoms as potential signs/symptoms of HIV infection. Such an examination should be repeated in each trimester or whenever patient symptoms suggest HIV infection. As more HIV-infected women are recognized, providers of obstetric care will need to become familiar with the common and uncommon manifestations of HIV infection and their treatment. The clinical assessment for HIV-infected individuals and the findings suggesting progression to symptomatic disease are outlined in Table 10.24. Of particular importance is careful assessment for lymphadenopathy and oral thrush.

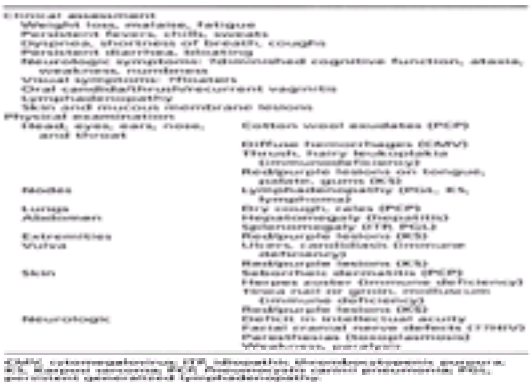


TABLE 10.24. ANTEPARTUM ASSESSMENT OF HIV-INFECTED WOMEN

Human immunodeficiency virus is a sexually and perinatally transmitted virus. Therefore, HIV-infected pregnant women (and nonpregnant as well) should be screened for other organisms with similar patterns of transmission (297,401,634), including the STDs, gonorrhea, syphilis, chlamydia, hepatitis B virus, and HSV. Because CMV and toxoplasmosis occur frequently in HIV-infected individuals and can result in serious consequences to the fetus, baseline antibody titers for these infections should be obtained to assist in the diagnosis if symptoms subsequently occur. *Mycobacterium tuberculosis* infection is common in HIV-infected persons and should be ruled out (297,401,634). Thus, tuberculosis skin testing should be performed as part of routine prenatal care in HIV-infected women. Two control antigens should be applied concomitantly because anergy may be present, especially in patients with low CD4 counts. In HIV-infected persons, 5-mm induration is considered a positive test. If the PPD is positive, a chest x-ray is undertaken. Alternatively, some authorities use chest x-rays (after first trimester) for all HIV-infected pregnant women regardless of their PPD status (634).

Pap smears to rule out CIN or cervical carcinoma should be performed. With report of an abnormal Pap smear, HIV-infected women should be evaluated immediately with colposcopy and directed biopsies as indicated. HIV-infected women who are severely immunosuppressed are at increased risk for developing CIN (647,648 and 649).

Physicians providing obstetric care need to be knowledgeable about the clinical management of HIV-infected pregnant women. To a large extent, management of HIV-infected pregnant women relies on determination of the HIV-1 RNA viral load and the $CD4^+$ lymphocyte count. The $CD4^+$ count provides an indicator of the degree of immunosuppression present. Pregnant women with a low CD4 count are at high risk for opportunistic infections and the risk of mortality from PCP. Plasma HIV viral load needs to be monitored closely during pregnancy (592,634). Quantification of HIV-1 RNA copy number (i.e., viral load) is a powerful tool for assessing HIV disease stage, risk for progression of HIV disease, and the effects of therapy (592). The PHS Task Force recommends that HIV-1 RNA should be monitored during pregnancy approximately once per trimester (592). Other investigators recommend once monthly or bimonthly monitoring if patients have undetectable plasma HIV-1 RNA levels and/or CD4 counts greater than 500/mm^3 (634). There are benefits of antiretroviral treatment and *P. carinii* prophylaxis to the health of HIV-infected women. Optimal antiretroviral therapy should minimize the risk of perinatal transmission of HIV (592). Although the care and treatment of the opportunistic infections associated with HIV infection in most instances will be coordinated with consultants familiar with the care of AIDS patients and/or with infectious disease specialists, obstetricians will need to be alert to suspect these infections. Moreover, providers of obstetric care should be aware of the common treatment regimens for HIV and HIV-associated infections and how these regimens may need to be modified during pregnancy. Antiretroviral therapy and treatment of opportunistic infections is discussed in the “Management and Prevention of HIV Infection” section. Although pregnancy may necessitate modification of treatment regimens, in most instances, the serious nature of these infections outweighs the risks associated with the agents used in these regimens (592).

Intrapartum Management of HIV-Infected Women

Early in the HIV epidemic, it was recommended that the obstetric management of HIV-infected women not be altered in any substantial way (650,651). More recently, better understanding of the pathogenesis of HIV infection, determination of risks associated with vertical transmission, and availability of effective antiretroviral therapy (monotherapy or combination therapy) have dramatically affected the intrapartum management of HIV-infected women. As discussed in the section on risk factors for perinatal HIV transmission, increasing duration of ROM (> 4 hours) has been associated with an increased risk of vertical transmission in women not receiving any antiretroviral therapy (536,537,609,613). Thus, the current recommendation is to avoid artificial ROM (if possible) in HIV-infected women in labor. The role of cesarean section in HIV-infected women with ROM ³4 hours remains to be determined. Among women treated with ZDV, some studies have shown that the risk of transmission increases with longer duration of ROM (559,610), whereas others have not (611,612). Determination of the importance of ROM ³4 hours in women undergoing HAART who have undetectable HIV-1 RNA levels requires elucidation.

The predominant timing of vertical HIV transmission is intrapartum, with either transplacental mother-fetal microtransfusion of blood containing HIV during contractions or through exposure to HIV in maternal cervicovaginal secretions and blood during labor and delivery (595). Theoretically, performing cesarean deliveries before the onset of labor and ROM could reduce the risk of vertical transmission in

HIV-infected mothers with high viral loads (595). Whereas early studies yielded inconsistent results on the relationship between mode of delivery and perinatal transmission of HIV, data from more recent investigations, including two prospective cohorts (633,652), a European collaborative prospective randomized study (594), and a meta-analysis of 15 prospective cohort studies with more than 7,800 mother-child pairs (593), demonstrate that elective (scheduled) cesarean delivery reduces the risk of vertical transmission of HIV compared to vaginal delivery or unscheduled cesarean sections. This was true whether or not the mother received ZDV (595). However, the risk of vertical transmission is directly proportional to the viral load of HIV. At very low concentrations of HIV-1 RNA in maternal plasma (<1,000 copies/mL), the observed incidence of vertical transmission in recent studies involving 141 mother-infant pairs was 0% (95% CI, 0%–2%) (559,611). Moreover, the evidence demonstrating reduction in vertical transmission rates comes from studies (593,594,633,650) that were performed largely before the use of HAART and did not include data regarding maternal viral load (595). Thus, whether cesarean delivery offers any benefit to women undergoing HAART or women with low or undetectable maternal viral loads is unknown (595,653).

In a cost-effectiveness study, Chen et al. (654) noted that elective cesarean delivery in HIV-infected women receiving ZDV to prevent vertical transmission is cost saving. However, if use of HAART and/or measurement of viral load result in at least 50% reduction of the baseline perinatal HIV transmission rates, elective cesarean delivery is not cost saving (654). In May 2000, The ACOG Committee Opinion 234 provided a set of recommendations for scheduled cesarean delivery to prevent vertical transmission of HIV (Table 10.25) (595). The PHS Task Force recommendations are in agreement regarding the role of scheduled cesarean delivery in decreasing the risk of vertical transmission (592). The use of antiretroviral therapy during the intrapartum period is discussed in the “Management and Prevention of HIV Infection” section.

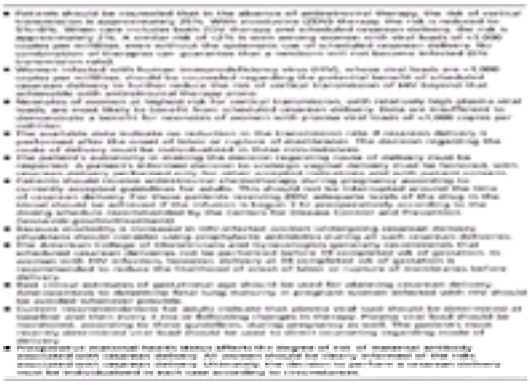


TABLE 10.25. AMERICAN COLLEGE OF OBSTETRICIANS GYNECOLOGISTS RECOMMENDATIONS FOR SCHEDULED CESAREAN SECTION AND THE PREVENTION OF VERTICAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Direct contact between maternal vaginal secretions infected with HIV and fetal blood

should be avoided as much as possible. Consequently, it has been suggested that fetal scalp electrodes and/or fetal scalp blood sampling not be used, but rather that external fetal monitoring be relied on whenever possible. Use of forceps and vacuum delivery in some studies has been associated with an increased risk of vertical transmission.

A second major concern during the intrapartum period is the prevention of the nosocomial spread of HIV to health care workers. In general, as discussed previously, the risk to health care workers from occupational exposures to patients infected with HIV is believed to be low (389,390,391,392,393,394,395,396,397,398,399 and 400).

Hagen and colleagues (655) assessed the risk of a surgeon to acquire HIV during an operative procedure. The estimated risk of a surgeon operating on an HIV-infected patient ranges from 1:4,500 to 1:130,000. If the patient is at low risk for HIV infection, the surgeon's risk ranges from 1:450,000 to 1:1.3 billion. It is crucial to treat the body fluids of all patients as potentially infected, not only with HIV but also with CMV, hepatitis B virus, and other blood-borne infectious organisms. This concept forms the basis for the recommendation that “Universal Blood and Body Fluid Precautions” be used to reduce the risk of nosocomial spread of such infectious agents to health care workers (656). These precautions include the use of gloves for procedures in which contact with blood or other body fluids or tissues might occur; the use of masks and protective eyewear when splatter or aerosolization of body fluids may occur; and the use of gowns or other protective garments when clothing is likely to be soiled. In addition, resheathing, bending, or breaking of needles should be avoided; puncture-resistant disposal containers should be used for needles and syringes; and designated infected waste disposal bags and containers should be available. Although the risk of HIV transmission to health care workers appears to be low, the standard guidelines set forth by the CDC should be followed in labor and delivery areas (656). Specific infection control methods in labor and delivery suites include

1. Use of water-resistant gowns and gloves during deliveries
2. Use of gloves while handling the neonate while maternal secretions are present
3. Frequent hand-washing after procedures and/or patient contact
4. Use of protective eyewear for deliveries
5. Handling of placentas with gloves and labeling of placentas as infectious waste.

Suction devices that use mouth suction to clear the neonatal airway (e.g., DeLee suction devices) should not be used; rather, devices hooked up to wall suction are recommended. Although the general guidelines only recommend use of a mask if a contagious airborne infection such as tuberculosis is present (or suspected), the splashing of blood at delivery is almost inevitable and masks should be worn at all births. Finally, if exposure to body fluids suspected or known to be infected with HIV occurs, counseling, antibody testing, and prophylaxis with antiretroviral therapy should be considered (see section on management and prevention of HIV infection).

Postpartum Management of HIV-Infected Women

During the postpartum period, the same infection control guidelines based on the “Universal Blood and Body Fluid Precautions” should be adhered to. In particular, care in handling perineal pads, lochial drainage, and incisions (episiotomy or

abdominal wound) is required. There is no rationale for separating the HIV-infected mother from her infant, and the HIV-infected mother should be allowed full access to her infant. Very little information is available regarding the immediate postpartum course of HIV-infected women. Selwyn et al. (476) reported that the rate of amnionitis/endometritis in HIV-seropositive IDU mothers was similar to that seen in seronegative IDUs. Postpartum, newly identified HIV-infected mothers should be referred to physician(s) experienced and knowledgeable in the management of HIV infection. It is critical that coordination of maternal and neonatal care and support be undertaken.

The newborn will require close follow-up and evaluation by a pediatrician(s) familiar with the care of infants with HIV infection. Use of gloves and hand-washing for contact with blood and/or body fluids of such newborns should be standard practice. Live virus vaccines should be avoided until the infant has been demonstrated to not be infected. Cord blood contains maternal antibody, and the infant can maintain levels of maternal antibody for up to 15 months. Thus, infants of HIV-infected mothers should be tested sequentially for HIV antibody until it is documented that the infant is either antibody negative, or until after 15 months, at which time the presence of antibody reflects HIV infection in the baby. Detection of HIV by culture, PCR, or antigen in the infant at any age is proof of HIV infection.

Management And Prevention Of HIV Infection

The management of nonpregnant and pregnant women with HIV infection, including treatment of opportunistic infections, will be summarized in this and the following section. This section will briefly discuss the use of ZDV (azidothymidine [AZT]) and other antiretroviral agents for the management of patients with HIV infection and the principles for prevention of HIV infection.

Zidovudine was the first antiretroviral drug to be licensed in the United States for treatment of patients with HIV infection. Although initially approved for treatment of AIDS and advanced AIDS-related complex, ZDV also is approved for management of adults with asymptomatic HIV infection who have evidence of impaired immunity (CD4 cell count £500/mm^3) and HIV-infected children. Zidovudine is a thymidine analogue that is an inhibitor of the RT enzyme of HIV and has been demonstrated to reduce the rate of HIV replication *in vitro* (657). In the initial multicenter collaborative clinical trial in patients with AIDS and opportunistic infections, ZDV was demonstrated to reduce the frequency and severity of opportunistic infections and resulted in a significant reduction in early mortality (658). The study was ended prematurely because of the quickly recognized advantage accruing to patients receiving ZDV. Not only was improvement seen in clinical well-being, but HIV p24 antigen levels were reduced in patients undergoing therapy. A brief (2-month) rise in CD_4 cell counts occurred, but it was not sustained. Creagh-Kirk et al. (659) assessed a much larger group of 4805 patients receiving ZDV in a compassionate plea program and confirmed the reduction in early mortality and the reduction in frequency and severity of opportunistic infections.

After the introduction in 1996 of more potent antiretroviral agents and the concept of combination therapy, the treatment of HIV-infected patients changed remarkably. In an attempt to guide clinicians in the treatment of HIV-infected patients, two panels of experts have been established that set guidelines for the treatment of persons with

HIV infection (364,365,660). The Department of Health and Human Services in the Henry J. Kaiser Family Foundation has developed guidelines for the management of HIV infection (365). In addition, specific recommendations for antiretroviral therapy have been developed by the International AIDS Society-USA; these recommendations are updated annually. The abbreviated chemical, generic, and trade names for the currently available antiretroviral agents are listed in Table 10.26. The three major categories include nucleoside RT inhibitors (NRTIs), non-nucleoside RT inhibitors (NNRTIs), and protease inhibitors.

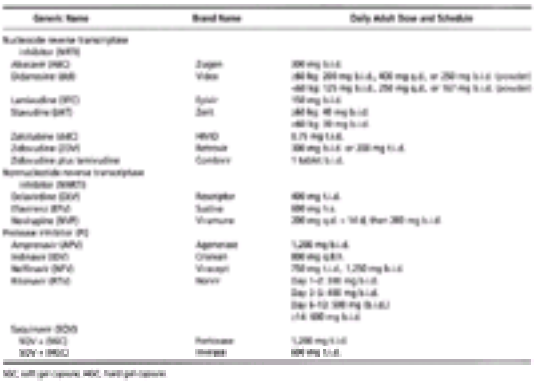


TABLE 10.26. ANTIRETROVIRAL MEDICATIONS

In 1996, two important studies (ACTG 175 and Delta Trials) demonstrated that NRTI combination therapy was more beneficial than monotherapy (661,662). These trials compared ZDV combined with didanosine (ddI) or zalcitabine (ddC) with ZDV or DDI monotherapy. After introduction of protease inhibitors in 1996 and publication of the ACTG 320 study in 1997, it was obvious that combination therapy with a protease inhibitor was superior to dual NRTIs alone (663). After the introduction of protease inhibitors, there were dramatic improvements in both mortality and the incidence of opportunistic infections associated with HIV infection (664,665). Combination therapy that included a protease inhibitor yielded rapid reductions in the amount of virus present in blood. The goal of therapy at the present time is to achieve viral loads below the level of quantitation; with commercially available testing, the most sensitive tests detect as few as 20 copies/mL (666). The significant reduction in viral loads is associated with substantial increases in CD4 cell counts, resolution and decline in incidence of opportunistic infections, reductions in hospitalization, and lower mortality (665,667).

The overall goal of antiretroviral therapy is to maintain viral suppression for as long as possible (668). Therapy that reduces HIV-1 RNA levels to below the limits of detection with a concomitant and usually large increase in CD4 counts has been called highly active antiretroviral therapy (HAART) (666,668). Initially, HAART was a combination of a protease inhibitor with two NRTIs, but it now includes other combinations that suppress HIV RNA levels to below the limits of detection. Examples include dual nucleoside therapy and efavirenz (NNRTI) and triple NRTI combinations such as ZDV, 3TC, and abacavir (Table 10.27). With the introduction of HAART, there was optimism that the production of significant viral decay would lead

to viral eradication after a few years of therapy. However, it became increasingly clear that viral replication continues in resting CD4 cells and macrophages in patients undergoing HAART. Viral replication has been demonstrated in lymph nodes and large volumes of blood; latent HIV also exists in cells despite HAART reduction in plasma HIV RNA levels (669,670). These studies demonstrating persistence of latent virus despite several years of therapy have led to diminishing optimism that viral eradication would be possible without the need for lifelong antiretroviral therapy (666).

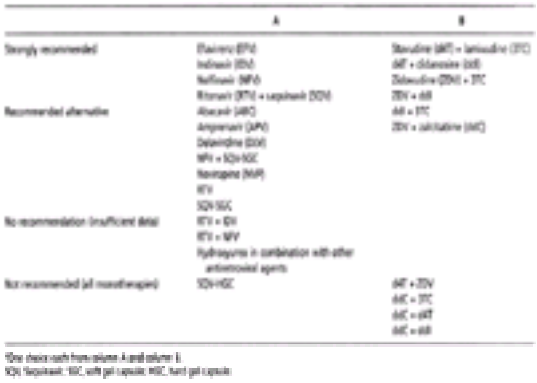


TABLE 10.27. RECOMMENDED ANTIRETROVIRAL REGIMENS FOR INITIAL TREATMENT OF ESTABLISHED HUMAN IMMUNODEFICIENCY VIRUS INFECTION[a]

Both the International AIDS Society-USA and the Department of Health and Human Services Guidelines contain specific recommendations for initiation of treatment based on the patient's CD4 counts and viral loads (658,659 and 660). Therapy is recommended for all symptomatic patients regardless of viral load or $CD4^+$ T-cell count. In addition, patients who are asymptomatic with CD4 counts less than 350 to 500 cells/mL or plasma HIV-1 RNA levels greater than 10,000 to 20,000 copies/mL should begin treatment. As reviewed by Deeks and Volberding (668), these recommendations are derived from the observation that viral load is a strong independent predictor of disease progression and that the durability of the virologic response to therapy is greater when therapy is initiated at an earlier stage of HIV disease. In addition, early intervention helps prevent the irreversible immunologic damage and the development of multiviral quasi-species. In HIV-infected patients who are asymptomatic with CD4 counts greater than 500 cells/mL and HIV-1 RNA levels greater than 10,000 copies, experts recommend that therapy be delayed while close monitoring is continued (658). Table 10.28 provides the guidelines from the CDC and the International AIDS Society-USA for initiation of antiretroviral therapy.

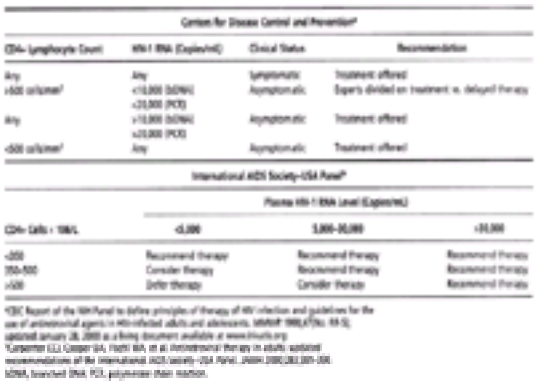


TABLE 10.28. GUIDELINES FOR INITIATING ANTIRETROVIRAL THERAPY

In general, the results of numerous studies involving combination regimens demonstrated that the use of three agents is superior to the use of two agents in suppressing viral replication (668). As noted by Deeks and Volberding (668), the particular three-drug (or four-drug) regimen used for initial therapy probably depends on the patient's individual preference and disease stage. As can be seen in Table 10.27, a variety of antiretroviral regimens combining nucleoside analogues with protease inhibitors or NNRTIs are available. Most commonly recommended for initial treatment are (i) protease inhibitor and (ii) NRTIs or efavirenz (NNRTI) and two NRTIs (666). Among the factors that must be considered in making this initial choice are (i) likelihood of patient adherence to the regimen, (ii) potential for long-term side effects, (iii) preservation of future treatment options, and (iv) potential for drug interactions with other medications (666). Thus, it is important that therapy be individualized based on these factors. As discussed by Deeks and Volberding (668), there is no clear consensus on the best third drug to use in these combination regimens. In asymptomatic naive patients with CD4 T-cell counts greater than 200 cells/mL^3, two nucleoside analogues and either a protease inhibitor or NNRTI is appropriate. In favor of the NNRTI-based regimen is the ease of dosing NNRTIs, which results in increased adherence, lack of long-term protease inhibitor-related toxicities (i.e., lipodystrophy), and preservation of second-line salvage regimens (i.e., protease inhibitor-based regimens). On the other hand, in favor of the protease inhibitor-based regimen as initial therapy is that protease inhibitors may be more potent and that long-term data are available demonstrating the efficacy of protease inhibitor-based therapy and suppressant viral replication in prolonging life. This increased potency/efficacy has led many to recommend that, at least in patients with more advanced disease, protease inhibitor-based regimens should be used (668).

Unfortunately, the initial hope that HAART would maintain viral suppression for many years has not been fulfilled, and virologic failure is common (668). Initiation of second-line therapy in the face of failure with initial antiretroviral therapy is a complex scenario that requires consultation with an HIV specialist knowledgeable and experienced with such situations. The Department of Health and Human Services and the International AIDS Society-USA have provided general guidelines to be followed (660,671). As reviewed by Deeks and Volberding (668), these guidelines include (i) establishment of the reason for failure (i.e., lack of compliance); (ii) recognition that cross-resistance is common within each class of antiretroviral

agents; (iii) changing all drugs simultaneously to a regimen containing three or more drugs to which the patient is naive; and (iv) switch to a new regimen should take place immediately to prevent ongoing viral replication that would select for higher levels of resistance (668). Detailed description of the use of HAART is beyond the scope of this chapter. There are several excellent reviews of this subject for interested readers (666,668,672,673 and 674).

Antiretroviral Drugs in Pregnant HIV-Infected Women

The PHS Task Force recently revised its recommendations for its use of antiretroviral drugs in pregnant HIV-infected women (592). The treatment recommendations for pregnant women infected with HIV have been based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus, or infant and unless these adverse effects outweigh the benefit to the women (675). As discussed earlier in nonpregnant patients, combination antiretroviral therapy generally consisting of two nucleoside analogue RT inhibitors and a protease inhibitor is the recommended standard for HIV-infected adults (624). The PHS Task Force emphasizes that pregnancy should not preclude the use of optimal therapeutic regimens. However, there are unique considerations that must be addressed when choosing antiretroviral drugs for the treatment of HIV-infected pregnant women, including (i) potential changes in dosing requirements secondary to the physiologic changes of pregnancy; (ii) potential effects of antiretroviral drugs in pregnant women; and (iii) potential short-term and long-term effects of the antiretroviral drug(s) on the fetus and newborn. These effects may not be known for many of the newer antiretroviral drugs for which there is limited experience in pregnancy. The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing with her health care provider the known and unknown benefits and risks to her and the fetus (592). Table 10.29 reviews the limited data on placental passage and long-term animal carcinogenicity for FDA-approved antiretroviral drugs. The goal of antiretroviral therapy in pregnancy is twofold: (i) to optimize the maternal health of HIV-1 infected women, and (ii) to reduce perinatal HIV-1 transmission. As discussed in the section on risk of perinatal transmission of HIV, both monotherapy with ZDV and combination antiretroviral therapy provided during antepartum, intrapartum, and postpartum to the neonate have been demonstrated to be effective in reducing vertical transmission of HIV (592). Similarly, shorter courses involving only intrapartum and postpartum therapy also have been studied and shown to be reasonably effective in reducing vertical transmission (592). The PHS Task Force recommends that offering antiretroviral therapy to HIV-infected pregnant women during pregnancy should be accompanied by discussion of known and unknown short-term and long-term benefits and risks of such therapy for infected women and infants. Standard antiretroviral therapy should be discussed with, and offered to, HIV-infected pregnant women. To prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into the antiretroviral regimen.

TABLE 10.29. PRECLINICAL AND CLINICAL DATA RELEVANT TO USE OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Health care providers caring for HIV-infected pregnant women who are receiving protease inhibitor therapy need to be aware of the potential for hyperglycemia. Not only hyperglycemia but new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported in association with use of protease inhibitor antiretroviral drugs in HIV-infected patients (676,677,678 and 679). Nucleoside analogue drugs are known to induce mitochondrial dysfunction (592). The cause of this dysfunction is the affinity of these drugs for mitochondrial g DNA polymerase, which can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction (680). Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis (592). For more detailed discussion of mitochondrial toxicity, the reader is referred to the PHS Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States (592).

The PHS Task Force recommendations for the use of antiretroviral chemoprophylaxis to reduce the risk for perinatal transmission are based on various clinical scenarios that commonly may be seen in clinical practice (592). Current data indicate that the PACTG 076 ZDV regimen also is effective for women with advanced disease, low CD4 count, and previous CDC therapy. Clinical scenarios that are discussed do not stratify by CD4 total or prior ZDV use. Similarly, because current data indicate most transmission occurs near the time of or during delivery, ZDV chemoprophylaxis is recommended regardless of gestational age, and no stratification according to gestational age is included in the recommendations. Although the original ZDV studies used 100-mg administered orally five times daily during the antepartum period, the current standard ZDV dosing regimen for adults is 200 mg three times a day or 300 mg twice daily.

For HIV-infected pregnant women who have not received prior antiretroviral therapy, the recommendations for initiation and choice of antiretroviral therapy are based on the same parameters used for persons who are not pregnant. Obviously, the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed (592,624). The three-part ZDV chemoprophylaxis regimen

(Table 10.21) initiated after the first trimester should be recommended for all HIV-infected pregnant women to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of maternal HIV infection is recommended for those women whose clinical, immunologic, or virologic status requires treatment and should be strongly considered for any infected women with HIV RNA level greater than 1,000 copies/mL regardless of clinical or immunologic status (Table 10.28). The task force suggests that women in the first trimester of pregnancy consider delaying initiation of therapy until after 10 to 12 weeks of gestation. They suggest this delay in part because of unknown effects on the fetus and because the nausea and vomiting of early pregnancy may interfere with compliance, which would lead to suboptimal therapy and increasing risk for development of resistant virus. An HIV-infected woman receiving antiretroviral therapy previously in pregnancy whois identified after the first trimester should continue therapy. Whenever possible, zidovudine should be a component of the antenatal antiretroviral treatment regimen after the first trimester.

The woman receiving antiretroviral therapy in pregnancy who is recognized during the first trimester should be counseled regarding the benefits and potential risks of antiretroviral administration during this period and continuation of therapy. If a decision is made to discontinue therapy during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid development of drug resistance. Regardless of the intrapartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the neonate. For HIV-infected women in labor who underwent no prior antiretroviral therapy, several effective regimens are available, including (i) single-dose nevirapine at the onset of labor, followed by a single dose of nevirapine for the newborn at age 48 hours; (ii) oral ZDV and 3TC during labor, followed by 1 week of oral ZDV/3TC for the newborn; (iii) intrapartum intravenous ZDV, followed by 6 weeks of ZDV for the newborn; and (iv) two dose of the nevirapine regimen combined with intrapartum intravenous ZDV and 6 weeks of ZDV for the newborn (592). These women should have appropriate assessments, including CD4 count and HIV-1 RNA copy number, to determine whether antiretroviral therapy is recommended following delivery. In infants born to mothers who did not receive antiretroviral therapy during pregnancy or intrapartum, the task force recommends that the 6-week neonatal ZDV component be discussed with the mother and offered for the newborn. Zidovudine should be initiated as soon as possible after delivery (preferably within 6 to 12 hours of birth). Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if mother is known or suspected to have ZDV-resistant virus.

The HIV-infected pregnant woman should be monitored according to the same standards for monitoring HIV-infected persons who are not pregnant (592). Such monitoring includes measurement of CD4 T-lymphocyte counts and HIV-1 RNA levels approximately every trimester (i.e., every 3 months) to determine (i) the need for antiretroviral therapy of maternal HIV-1 disease; (ii) whether such therapy needs to be altered; and (iii) whether prophylaxis against PCP or other opportunistic infections should be initiated. Monitoring for potential complications of administration of antiretroviral agents should be based on what is known about the side effects of the drugs the pregnant woman is receiving (e.g., routine hematologic and liver enzyme monitoring for ZDV and monitoring for development of hyperglycemia in women receiving protease inhibitors).

Opportunistic Infections

Opportunistic infections are the hallmark indicator of the immunodeficiency that characterizes HIV infection as it progresses to symptomatic disease. A detailed description of the manifestations and treatment of the opportunistic infections associated with HIV infection is beyond the scope of this chapter. The more common infections are summarized briefly here. The reader interested in a more detailed discussion is referred to recent reviews of the manifestations and treatment of these diseases (681,682,683 and 684).

Prior to the availability of effective antiretroviral therapy, the primary strategy in managing patients with AIDS was prevention of opportunistic infections (683). To this end, prevention strategies were developed for many of the major opportunistic infections, including PCP, disseminated MAC disease, and cerebral toxoplasmosis. These prophylactic therapies became the recommended standard of care for immunosuppressed and susceptible HIV-infected patients (681,682,683 and 684). Although routine prophylaxis was not recommended for fungal infections and CMV disease, it ws used for selected patients with these opportunistic infections. Use of the recommended prophylactic management approaches (primary and secondary) led to a decline in the incidence of these opportunistic infections (683). An even more dramatic decline in the incidence of opportunistic infections has occurred with the availability of effective monotherapy and, to a greater extent, HAART (Fig. 10.8) (681,682,683,684 and 685). This decline in opportunistic infections has resulted in a decrease in HIV-associated mortality (684,685). Thus, in the era of HAART, the initial step in prevention of opportunistic infections is the use of potent antiretroviral therapy that not only reduces the HIV-1 RNA viral load, but also results in repair and recovery of the immune system (683).

The most common opportunistic infection seen in patients with HIV infection is PCP. In a review of pregnancy-associated deaths due to AIDS in the United States, Koonin et al. (496) noted that most of these deaths were due to PCP. *Pneumocystis carinii* pneumonia is the most common AIDS-defining disease. It has a high mortality rate of 5% to 20% and a high rate of recurrence in those patients not receiving prophylaxis (686). Current standard treatment is trimethoprim-sulfamethoxazole (TMP-SMX) (Table 10.30). Both sulfamethoxazole and trimethoprim cross the placenta. However, neither has been documented to be teratogenic in humans (687). Although a theoretical risk exists for hyperbilirubinemia and kernicterus with sulfonamide use close to delivery, the risks of PCP to the pregnant woman far outweigh these potential risks to the fetus.

TABLE 10.30. PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Primary prophylaxis against PCP is recommended for adults and adolescents who have HIV infection (including pregnant women and those receiving HAART) if they have a $CD4^+$ T-lymphocyte count less than 200/mL or a history of oral pharyngeal candidiasis (681). Patients with a CD4 percentage less than 14% or a history of AIDS-defining illness but who do not otherwise qualify should be considered for prophylaxis. Trimethoprim-sulfamethoxazole is the recommended prophylactic agent. One double-strength tablet per day is the preferred regimen. For patients who cannot tolerate TMP-SMX, alternatives include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respirgard II nebulizer (Marquest, Inglewood, CO), and atovaquone (681). As reviewed by the USPHS/IDSA guidelines, several studies have suggested that PCP prophylaxis can be discontinued safely in patients responding to HAART with a sustained increase in CD4 counts from less than 200 cells/mL to more than 200 cells/mL. In addition, many of these patients had a sustained suppression of HIV-1 RNA levels (681). Thus, it is suggested that providers may wish to discontinue prophylaxis when patients have a sustained CD4 T-lymphocyte count greater than 200 ml for at least 3 to 6 months and a sustained reduction in viral load for at least 3 to 6 months (681). For secondary prophylaxis or prevention of recurrence, adults and adolescents with a history of PCP should be administered chemoprophylaxis with the regimens described for primary prophylaxis (681). Currently it is not recommended that patients receiving secondary prophylaxis have their prophylaxis discontinued even when their CD4 counts are greater than 200 ml cells. Chemoprophylaxis for PCP is recommended for pregnant women as is recommended for other adults (681). In pregnancy, TMP-SMX is the recommended prophylactic agent, with dapsone as the alternative.

Prolonged and persistent episodes of severe herpes simplex infection can occur in HIV-infected patients. Acyclovir therapy has been very effective in shortening the duration and decreasing the severity of episodes in nonpregnant AIDS patients. Although the safety of acyclovir in pregnancy has not been fully established, it has been used in pregnancy for non-AIDS patients with good results and safety in limited numbers of patients. Some authorities suggest the prophylactic use of acyclovir (400 mg orally three times a day) in pregnant HIV-infected women who have had a recurrence of genital herpes during pregnancy or who are seropositive for HSV type

2 (634). The recommended dosing for type of HSV infection is given in Table 10.30.

The most common fungal infection occurring in HIV-infected patients is oropharyngeal candidiasis. The recommended treatment for oropharyngeal candidiasis is given in Table 10.30. Rhoades et al. (688) reported that women infected with HIV often present with chronic vaginal candidiasis. Recurrent or persistent vaginal candidiasis is a category B disease according to the new CDC classification scheme (198). Although vaginal candidiasis is not a major perinatal concern, recurrent severe symptoms in the mother may require a therapeutic and prophylactic course of oral ketoconazole or fluconazole (Table 10.30). Patients receiving this ketoconazole therapy should have their liver function tests closely monitored.

Toxoplasmosis is a common cause of central nervous system symptoms in AIDS patients. Thus, HIV-infected individuals who develop focal neurologic findings, changes in sensorium, and fever should be evaluated for the presence of toxoplasmosis. Infection with *Toxoplasma gondii* early in pregnancy can result in stillbirth or congenital toxoplasmosis with microcephaly, chorioretinitis, mental retardation, and/or neurosensory hearing loss (689). Routine serologic screening for toxoplasmosis is recommended for HIV-infected pregnant women at their initial prenatal visit. If seroconversion is documented and confirms acute toxoplasmosis, sulfadiazine (1 g orally four times a day) and pyrimethamine isethionate (25 to 50 mg orally once day) should be administered after the mother receives counseling about potential fetal risks and agrees to therapy. Although percutaneous umbilical cord sampling has been used to document fetal toxoplasmosis in non–HIV-infected patients (690), concerns of inoculating the fetus with maternal blood infected with HIV has precluded the use of this option in HIV-infected women.

Guidelines for the management and prevention of acute or primary toxoplasmosis encephalitis and maintenance treatment are listed in Table 10.30. Primary prophylaxis is indicated for toxoplasma-seropositive patients who have a $CD4^+$ T-lymphocyte count less than 100/mL to prevent toxoplasmic encephalitis (681). The double-strength tablet daily dose of TMP-SMX is the preferred regimen for prevention of toxoplasmic encephalitis as it is for PCP prophylaxis (681). Alternatives in patients who cannot tolerate TMP-SMX are dapsone-pyrimethamine or atovaquone with or without pyrimethamine. As with PCP, limited data suggest that discontinuing prophylaxis against toxoplasmic encephalitis when CD4 counts rise above 100 cells/mL in response to antiretroviral therapy is associated with a low risk for toxoplasma encephalitis. Those patients who have had toxoplasma encephalitis should be administered lifelong suppressive therapy (secondary prophylaxis) with drugs active against toxoplasma to prevent relapse (681). A combination of pyrimethamine plus sulfadiazine and leucovorin generally is recommended (681). For patients who cannot tolerate sulfa drugs, a combination of pyrimethamine plus clindamycin is the alternative (681). For pregnant HIV-infected women, TMP-SMX is administered for prophylaxis. This is true for primary or secondary prevention. There have been rare reports of HIV-infected pregnant women with serologic evidence of remote toxoplasmic infection who have transmitted toxoplasmosis to their fetus *in utero* (681).

Cytomegalovirus disease can occur in HIV-infected individuals. Of particular concern is CMV retinitis, which is a common and potentially disabling (blindness) complication in AIDS patients. Less frequently, CMV colitis, esophagitis,

pneumonitis, and encephalitis are seen. Agents with demonstrated efficacy against CMV retinitis in AIDS include ganciclovir, foscarnet, and cidofovir (Table 10.30) (681). Prophylaxis with oral ganciclovir should be considered for HIV-infected patients who are CMV seropositive and who have a CD4 count less than 50 cells/mL (681). Practitioners should be aware of, and on the alert for, ganciclovir-induced neutropenia and anemia. The USPHS/IDSA guidelines stress that the most important method for preventing severe CMV disease is recognition of the early manifestations of the disease. Patients should be made aware of the significance of findings such as increased floaters in the eye and should be advised to check their visual acuity on a regular basis (i.e., by reading newsprint). In addition, regular funduscopic examinations by an ophthalmologist is recommended. It is important to recognize that CMV disease is not cured with courses of the currently available antiviral agents (e.g., ganciclovir, foscarnet, or cidofovir). Induction therapy should be followed by secondary prophylaxis for life (681). Regimens that are effective for chronic suppression include parenteral or oral ganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and, for retinitis, only ganciclovir administration via intraocular implants plus oral ganciclovir (681). Secondary prophylaxis may be stopped when the CD4 counts rise above 100 to 150 cells/mL and when HIV-1 RNA levels have been suppressed in response to HAART (681).

Tuberculosis now is recognized as an important HIV-associated infection. The current recommendations for tuberculosis treatment in HIV-infected patients are given in Table 10.30. Patients diagnosed with HIV infection should receive a tuberculin skin test (TST). All HIV-infected persons who have a positive TST result (³5 mm of induration) should undergo chest radiography and clinical evaluation to rule out active tuberculosis (681). All HIV-infected persons who have a positive TST result but have no evidence of active tuberculosis and no history of treatment or prophylaxis for tuberculosis should be administered preventive chemotherapy. Among the regimens recommended are isoniazid daily or twice weekly for 9 months or 2 months of therapy with either rifampin and pyrazinamide or rifabutin and pyrazinamide (681). Persons infected with HIV are at risk for peripheral neuropathy; therefore, they should also receive pyridoxine when they are given isoniazid. Providers should be cognizant of the fact that regimens containing rifampin or rifabutin have potential interaction, especially with protease inhibitors and NNRTIs. Persons infected with HIV who are close contacts of individuals who have infectious tuberculosis also should be administered preventive therapy regardless of the TST result or prior courses of chemoprophylaxis (681). For persons exposed to isoniazid-resistant and/or rifampin-resistant tuberculosis, the decision to use chemoprophylactic antimicrobacterial agents other than isoniazid alone, rifampin plus pyrazinamide, or rifabutin plus pyrazinamide should be based on the relative risk for exposure to resistant organisms and should be made in consultation with experts in the field. Unlike many of the other opportunistic infections, chronic suppressive therapy for a patient who has successfully completed a recommended regimen of treatment for tuberculosis is not recommended (681). In pregnant HIV-infected women, chemoprophylaxis for tuberculosis is recommended for patients who have either a positive TST result or history of exposure to active tuberculosis, after active tuberculosis in the patient has been excluded (681). A chest x-ray should be obtained before treatment, ensuring that appropriate abdominal pelvic lead apron shields are used. Except in instances of exposure to drug-resistant tuberculosis, isoniazid given daily or twice weekly is the prophylactic regimen of choice in pregnancy. This should be accompanied by pyridoxine to reduce the risk of

neurotoxicity.

Disseminated MAC infection has emerged as one of the most important opportunistic infections associated with AIDS. The recommended treatment for MAC disease is given in Table 10.30. Primary prophylaxis for prevention of disseminated infection with MAC should be provided to all HIV-infected persons with a CD4 T lymphocyte count of less than 50 cells/mL (681). Clarithromycin or azithromycin is the preferred prophylactic agent (Table 10.30). In addition to their preventive activity for MAC disease, clarithromycin and azithromycin protect against respiratory bacterial infections (681). If patients cannot tolerate either of these agents, rifabutin is the alternative prophylactic agent for MAC disease. Primary prophylaxis against MAC disease can be discontinued in persons receiving HAART who have an increase in their CD4 count to greater than 100 cells/mL for a sustained period (e.g., more than 3 to 6 months) and a sustained suppression of HIV-1 RNA viral levels (681). Persons infected with HIV who have been treated for disseminated MAC disease should receive full therapeutic doses of antimicrobacterial agents for life (681). For this purpose, clarithromycin or azithromycin is recommended in combination with ethambutol (681), which may be given with or without rifabutin. Pregnant HIV-infected women should receive chemoprophylaxis for MAC disease similar to that recommended for nonpregnant adults (681). Clarithromycin has been demonstrated to be teratogen in animals and should be used with caution during pregnancy. In pregnancy, azithromycin plus ethambutol is the preferred regimen for secondary prophylaxis (681).

For discussion of the management and prevention of other less common opportunistic infections, such as cryptococcosis, histoplasmosis, coccidioidomycosis, varicella-zoster, human herpesvirus type 8, hepatitis C, bacterial respiratory infection (e.g., *S. pneumoniae, H. influenzae*), and *Bartonella* infection (formerly *Rochalimaea*), which is transmitted from cats to severely immunocompromised HIV-infected persons, the reader is referred to the USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus (681).

Management of Health Care Workers Exposed to HIV

The CDC conducted a retrospective case-control study that assessed the occurrence of occupational HIV infections in health care workers (401). This study identified five factors associated with an increased risk for occupation infection with HIV: deep injury; visible blood on the device causing injury; injury with a needle that had been placed in the source patient's artery or vein; advanced HIV disease (surrogate for high viral load); and lack of ZDV postexposure chemoprophylaxis (401,691). In addition, administration of postexposure ZDV was associated with a nearly 80% reduction in the risk for occupational HIV infection (691). Subsequent to these findings, the USPHS published recommendations for postexposure prophylaxis (692). These recommendations are summarized in Table 10.31.

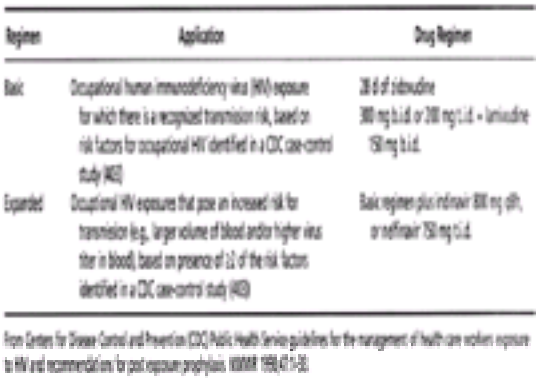


TABLE 10.31. RECOMMENDATIONS FOR POSTEXPOSURE PROPHYLAXIS REGIMENS: HEALTH CARE WORKER EXPOSURE TO HUMAN IMMUNODEFICIENCY VIRUS

Immediate treatment following exposure of a health care worker provides decontamination of the exposure site. Skin should be washed with soap and water, and mucous membranes should be flushed with water (401,691). Next, the type of exposure and the HIV status of the source patient should be determined. In HIV-infected sources, this includes assessment of viral load and $CD4^+$ T-lymphocyte count. The health care worker should be counseled extensively regarding the risks for infection associated with occupational exposures and the potential risks and benefits of antiretroviral chemoprophylaxis (401,691).

Gynecologic Aspects of HIV Infection

With the increasing incidence of HIV infection in women, the major focus of attention has been on addressing issues related to pregnancy and prevention of pediatric AIDS. However, gynecologic disease also is being commonly encountered in women with HIV infection (423,688,689). Several gynecologic diseases may be altered by HIV infection (e.g., CIN, invasive cervical carcinoma, PID, syphilis, and vulvovaginal candidiasis) (423,688). In addition, these gynecologic diseases may be refractory to standard treatment, especially as immune function deteriorates. In 1993, the CDC revised classification system for HIV infection included several gynecologic diseases. In clinical category B (illnesses attributable to or complicated by HIV) are (i) persistent, frequent, or poorly responsive vaginal candidiasis; (ii) moderate or severe CIN; and (iii) PID. Clinical category C (AIDS-defining illnesses) includes (i) chronic HSV ulcers and (ii) invasive cervical cancer.

An increased frequency of HPV-related CIN was noted in women with immunosuppression secondary to renal transplantation (695). Similar findings were reported in studies of women with HIV immunosuppression. In a review of five studies with controls by Mandelblatt et al. (696), the odds of HIV-infected women having CIN was 4.9 times (95% CI, 3.0–8.2) greater than that of HIV-negative women. The frequency and severity of CIN is related to the degree of immunosuppression (697,698). Wright et al. (699) noted in a large study of 303 HIV-infected women with a 21% rate of CIN that 29% of women with $CD4^+$ cell

counts less than 200/mL had cervical dysplasia compared to 17% of women with $CD4^+$ counts greater than 500/mL ($p < 0.05$). Korn and Landers (423) reviewed 19 published reports that assessed the prevalence of CIN in HIV-infected women; of 728 HIV-infected women, 38% had dysplasia by Pap smear and 42% by cervical biopsy. Over half of these lesions were high grade. This summary review also demonstrated that the prevalence of CIN was related to severity of HIV disease; 64% in women with AIDS compared to 36% in women with asymptomatic HIV infection (OR, 1.8; 95% CI, 1.1–2.9) (423).

Although Maiman et al. (648) initially questioned the sensitivity of the Pap smear compared to colposcopy-directed biopsy, data from more recent studies confirm that the Pap smear has good sensitivity for detecting CIN lesions in HIV-infected women, equal to that seen in non HIV-infected women (700,701,702,703,704,705 and 706). Korn and coworkers (707) confirmed that the sensitivity of the Pap smear is not diminished in HIV-seropositive women. Thus, in its guidelines for screening of HIV-infected women, the CDC recommends that the Pap smear, and not colposcopy, be used for screening (708). Using a quantitative HPV DNA assay, Cohn et al. (649) demonstrated that quantitative measures of total HPV DNA and high-risk HPV DNA were strongly associated with any CIN ($p = 0.005$) and high-grade CIN ($p = 0.0006$). These authors concluded that HIV-infected women with at least mild immunosuppression have a high incidence of CIN and that those with high baseline HPV DNA levels may be at the highest risk for incident CIN (649). In a similar vein, Heard and coworkers (709) noted high-load HPV infection was twice as frequent in severely immunocompromised women (CD4 cell count <200 cells/mL) as in those with higher CD4 levels ($p = 0.002$). Furthermore, high-load HPV infection was associated with a high risk of cervical disease (OR, 16.8; 95% CI, 7.0–40.3), and the risk in severely immunocompromised women was tenfold greater than the risk in women with CD4 cell counts <200 cells/mL (709). Low-load HPV infection was a risk factor for CIN only in severely immunocompromised women (OR, 7.4; 95% CI, 1.3–43.0) (709).

In HIV-infected women, the clinical course of cervical dysplasia is characterized by a more rapid progression of disease and more frequent recurrences after therapy than in HIV-negative women (710,711 and 712). Conti et al. (710) reported that progression of untreated CIN was four times as frequent in HIV-infected women compared to HIV-negative women. Maiman et al. (711) noted that recurrence occurred in 39% of CIN cases treated with ablative or excisional therapy in HIV-infected patients compared to 9% in HIV-negative women, with failure routes being highest in patients with more severe immunosuppression. Wright and coworkers (712) reported that loop excision failed to eradicate CIN in 60% of HIV-infected women compared to 13% of HIV-negative women. Korn and Landers (423) recommended that HIV-infected women undergo Pap smear screening every 6 months, with colposcopic evaluation if the Pap smear reveals atypia or CIN. Consideration should be given to primary colposcopy in poorly compliant patients (423).

To date, preliminary studies suggest that the clinical course of PID may be altered by symptomatic HIV infection and that these patients have blunted local mucosal immune responses resulting in inadequate response to medical therapy (423,713,714,715,716,717,718,719 and 720). Johnstone et al. (713) assessed the lymphocyte populations of endometrial tissue in women with and without HIV infection. The endometrium in HIV-infected women had significantly more

leukocytes, which suggested that decreased local immunity in the endometrium could lead to increased susceptibility to PID (713). Several studies demonstrated that PID may have a different initial presentation and response to treatment in HIV-infected women (716,717). Hogesberg et al. (716) noted lower white blood cell counts and a trend toward greater surgical intervention in 15 HIV-infected patients compared to HIV-negative patients (p = 0.06). Korn et al. (717) reported that HIV-infected patients with PID had significantly lower white blood cell counts and required more surgical intervention. The increased need for surgery was not due to an increased incidence of tuboovarian abscesses. Korn et al. (717) and Kamenga et al. (720) noted that HIV-infected women with PID had more severe clinical illness, However, the response to therapy was noted to be unaffected by HIV infection (716,717,719,720). Cohen et al. (721), in a laparoscopic study of PID, reported that tuboovarian masses often associated with microorganisms other than *N. gonorrhoeae* and *C. trachomatis* were more common in HIV-infected women. Bukusi et al. (722), also using laparoscopy, assessed the effects of HIV on the clinical presentation, severity causal organisms, and response to ambulatory therapy of PID. Endometrial biopsy revealed that endometritis was more frequent in HIV-infected women than in seronegative women (OR, 3.0; 95% CI, 1.5–5.9). Infection with either *N. gonorrhoeae* or *C. trachomatis* was least common and BV was most common in HIV-infected women (722). Irwin et al. (723) demonstrated that more HIV-infected women had ultrasound confirmation of adnexal masses at enrollment (40.9% vs. 27.2%). However, the clinical response to CDC-recommended antibiotics was the same in HIV-infected and noninfected women (723). HIV seroprevalence has ranged from 6.7% to 22% in women with PID in the United States (715,716). Thus, counseling and testing for HIV infection should be offered to all women with PID.

Oral mucocutaneous candidiasis is seen commonly in HIV-infected men and women. Although not considered an AIDS-defining illness, vulvovaginal candidiasis appears in the CDC classification system for HIV infection as a condition whose course or management may be altered by HIV infection. Several studies have noted that vaginal candidiasis occurs more frequently in HIV-infected women (688,724,725). Rhoades et al. (688) reported that 7 (24%) of 29 HIV-positive women with severe immunosuppression had a history of chronic vaginal candidiasis, and all seven eventually developed oral thrush. Imam and coworkers (724) noted that new-onset or increased frequency of vaginal candidiasis occurred before other signs of immune compromise were present. Spinillo et al. (725) reported similar findings. Carpenter et al. (424) reported that chronic candidiasis was the most common presenting complaint with newly diagnosed HIV infection. Duerr and coworkers (726) reported that increased rates of yeast colonization and vaginitis were not seen in HIV-infected women before onset of immune compromise. Both vaginal colonization and symptomatic vaginitis increased with immune compromise, especially at CD4 counts less than 200 cells/mm^3 (726). The rates in HIV-infected women without immune compromise were equal to those seen in HIV-negative women. Shifrin et al. (727) confirmed this finding, noting that the risk of developing vulvovaginal candidiasis was increased 6.8 times in women whose CD4 counts were less than 200 cells/mm^3.

Studies have assessed the prevalence of multiple vaginal infections and lower genital tract infections in HIV-infected women (684,728,729). Cu-Uvin et al. (728) evaluated 851 HIV-seropositive compared to 434 HIV-seronegative women and noted that HPV infections were more prevalent in HIV-seropositive women (64% vs. 25%). Although other lower genital tract infections were common, they were not statistically increased in the HIV-positive women: BV was present in 35% versus 33%, trichomoniasis in 12% versus 10%, *C. trachomatis* in 4% versus 5%, candida

vaginitis in 3% versus 2%, and *N. gonorrhoeae* in 0.8% versus 0.3% (728). Helfgott et al. (729) compared the frequency of vaginal infections in HIV-infected women and an HIV-negative control population. Although they reported no significant association between HIV infection and STDs in general, they did identify significant associations between HIV infection and BV, vulvovaginal candidiasis, and trichomoniasis vaginitis (729). Minkoff and coworkers (684), in a large study evaluating the prevalence and incidence of a variety of gynecologic disorders in HIV-infected women, also noted that HIV-positive women were more likely to have prevalent vulvovaginal candidiasis (OR, 1.8; 95% CI, 1.0–3.25) and oncogenic HPV (OR, 3.79; 95% CI, 2.43–5.91). In the longitudinal follow-up with this cohort, they noted that their annual incidence rates in women infected with HIV were 4.0% for candidiasis, 22% for oncogenic HPV, 10.3% for trichomoniasis vaginalis, and 10.9% for infection with HSV (684). In addition, these authors noted that HIV-infected women were significantly more likely to have amenorrhea and genital warts.

It is clear that HIV has a significant impact on the gynecologic health and reproductive outcomes of women. This impact appears to be more pronounced in parallel with greater degrees of immunosuppression (423,688). It is critical that clinicians be aware that HIV-infected women require meticulous gynecologic care, which includes vigilance for the occurrence of lower genital tract infections and other gynecologic disorders. The importance of recognizing and treating lower genital tract infection was demonstrated by Wang and coworkers (730), who reported that vaginal HIV-1 levels decreased 3.2- and 4.2-fold after treating *Candida* and *Trichomonas,* respectively. These authors suggested that HIV transmission intervention strategies incorporating diagnosis and treatment of these infections warrant evaluation (730).

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11

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is an acute onset illness characterized by fever, multiorgan involvement, and hypotension (1,2). Toxic shock syndrome has been associated with three etiologic agents. Most frequently, TSS is a severe form of *Staphylococcus aureus* or *Streptococcus pyogenes* (group A b-hemolytic streptococcus) infection. *Clostridium sordellii* soft tissue infections also may produce a TSS-like illness.

Staphylococcal TSS is an acute and severe multisystem illness that was described initially by Todd et al. (3) in 1978 and widely recognized by the early 1980s (3,4,5,6,7,8,9,10,11 and 12). The disease is characterized by sudden onset of high fever, hypotension, vomiting, diarrhea, erythematous cutaneous rash that desquamates during recovery, and multiple organ involvement. Although first described in association with *S. aureus* in seven children (four girls and three boys) by Todd and colleagues (3) in 1978, TSS occurs predominantly in adults, especially women (5,7,12). Thus, the obstetrician-gynecologist must understand TSS in order to properly diagnose and treat this potentially life-threatening illness. During the early 1980s, the overwhelming majority of TSS cases occurred in association with menstruation; TSS not associated with menstruation now occurs as frequently (Fig. 11.1) (13,14,15,16,17 and 18). A unique *S. aureus* toxin—now called toxic shock syndrome toxin 1 (TSST-1)—is associated with almost all menstruation-related TSS cases and at least half of nonmenstrual TSS (NMTSS) cases (19,20,21 and 22).

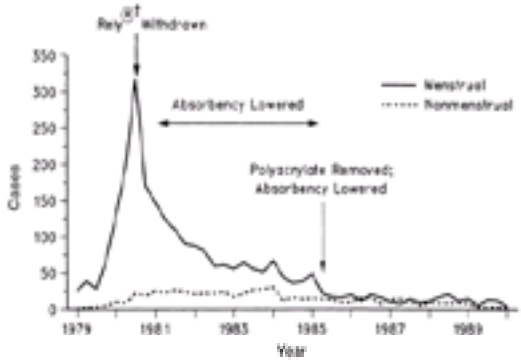


FIGURE 11.1. Reported cases of toxic shock syndrome by quarter in the United States, January 1, 1979 to March 31, 1990. *Includes only cases meeting the CDC case definition. †Use of trade names is for identification only and does not imply endorsement by the Public Health service or the US Department of Health and Human Services.

Since 1987, a syndrome known as streptococcal toxic shock-like syndrome has been described (1,2,23,24,25,26,27,28,29,30,31,32,33,34,35 and 36). Although group A streptococcus (*S. pyogenes*) causes common, usually clinically mild diseases such as pharyngitis and impetigo, it also is associated with uncommon but severe infections such as septicemia and pneumonia (32). As reported by Hoge et al. (31), invasive severe infections due to *S. pyogenes* remain relatively uncommon, but the clinical spectrum of these infections has changed significantly, particularly the appearance of clinical features resembling TSS caused by *S. aureus* (31,33,35). Streptococcal TSS is characterized by hypotension, marked systemic toxicity, rapidly progressive multisystem organ failure, and a high mortality rate of 30% to 60% (1,2,23,24,25,26,27,28,29,30,31,32,33,34,35 and 36).

Clostridium sordellii has been associated with a TSS-like illness (37,38,39,40,41,42,43 and 44). *Clostridium sordellii* TSS is characterized by the onset of gastrointestinal distress and generalized weakness in a previously healthy individual with a history of recent “clean” wounds or incisions followed by rapidly spreading edema that progresses to anasarca (44). Rapid deterioration in cardiovascular status with progressive, refractory hypotension ensues. Typically, no fever or hypothermia is present and minimal purulent discharge is present at the infection site.

EPIDEMIOLOGY

Staphylococcal Toxic Shock Syndrome

Shortly after Todd et al. (3) introduced the term toxic shock syndrome and defined the clinical criteria that distinguished TSS from similar diseases, a precipitous increase in the number TSS cases was reported in 1979 and early 1980 (4,7,12). By April 1982, 1,654 cases of TSS had been reported to the Centers for Disease Control

and Prevention (CDC). The peak number of reported TSS cases occurred from January to October 1980. Between 90% and 95% of cases occurred in women (5,7,12), with the greatest risk in women less than 30 years of age (5,12). The overwhelming majority (>95%) of menstruation-associated TSS cases occur in white women. Approximately 95% of TSS cases in women occurred in association with menstruation (1,2,4,5,7,11). Nearly 99% of women with menstruation-associated TSS wore tampons (5,8,45,46 and 47). At this peak time, the estimated incidence of TSS ranged from three to 15 cases per 100,000 menstruating women per year (5,7,8,12,48).

The CDC established national surveillance for TSS (16). Since 1980, with increased public awareness in tampon habits and absorbency, the estimated incidence of TSS has declined dramatically to a level of two to four cases per 100,000 women per year (Fig. 11.1). In 1980, there were 890 cases of TSS reported, of which 812 (91%) were associated with menstruation. By 1989, only 61 cases of TSS were reported, of which 45 (74%) were menstrual (16).

In 1980, the mortality rate for menstrual TSS (MTSS) was 5% (38/772); by 1988 and 1989, there were no deaths among women with MTSS (15). During this same period, reporting of nonmenstrual cases of TSS remained constant. A multistate active surveillance study in 1986 to 1987 confirmed the trends noted by the CDC's national passive surveillance (49). The study encompassed a population of 34 million persons and reported that the rate for MTSS was one per 100,000 women aged 15 to 44 years. This was a significant reduction from the rates reported in similar active surveillance reports in 1980, with rate of 6.2 per 100,000 in Wisconsin (7), nine per 100,000 in Minnesota (50), and 12.3 per 100,000 in Utah (51). Active surveillance also demonstrated that the proportion of TSS associated with menstruation had decreased substantially; by 1988, MTSS accounted for only 55% of cases of TSS (16,49).

The sudden increase in TSS cases reported in 1980 may have been the result of several factors: (a) the introduction of new tampon products, (b) changes in the constituent materials of tampons, and (c) a change in *S. aureus*.

A dramatic decrease in the number of menstruation-associated TSS cases reported to the CDC was noted following the removal of Rely® tampons from the market in September 1980 (Fig. 11.1) (52). However, using an active-passive surveillance system, Osterholm and Forfang (50) reported there was no decrease in the number of TSS cases in the state of Minnesota following the removal of Rely® tampons from the market. In addition, Davis and Vergeront (53) have suggested that TSS reporting may have been influenced by news media publicity related to TSS in the late summer and fall of 1980.

In a review of MTSS from 1980 to 1990, the CDC suggested that the principal reason for the decreased incidence of MTSS may be the decreased absorbency of tampons (16). They noted that in 1980, very high absorbency tampons (>15.4 g) were used by 42% of tampon users. In 1982, the United States Food and Drug Administration (FDA) required tampon package labeling advising women to use the lowest absorbency possible. As a result, by 1983 the proportion of very-high-absorbency tampons had decreased to 18% (54); by 1986, very-high-absorbency tampons were used by only 1% of women using tampons (16). In March 1990, the FDA commenced standardized absorbency labeling of tampons ranging from 6 to 15 g.

Very-high-absorbency tampons are no longer marketed in the United States.

Tampon composition also is an independent risk factor for TSS and has changed since 1980 (16). The Rely® tampon consisted of polyester foam and cross-linked carboxymethylcellulose, a combination no longer used in tampons. The unique composition of Rely® tampons may have been responsible for the significant increased risk for MTSS associated with that product (51). Polyacrylate-containing tampons were withdrawn from the market in 1985 (Fig. 11.1), resulting in a further decrease in reported cases of MTSS. Current tampons are manufactured from cotton and/or rayon (16).

Although reported cases of MTSS have declined substantially since the peak in 1980, reporting of NMTSS has remained constant during this time (16). Now nearly one half of TSS cases are nonmenstrual, up considerably from the 6% of TSS cases not associated with menstruation prior to 1981 (45). As suggested by Duff (55), this increase probably is due to two factors: (i) a change in the patterns of tampon use, and (ii) improved recognition of TSS in a variety of clinical settings. As reported by Reingold and coworkers (13), patients with TSS not associated with menstruation differ significantly in age and racial distribution from those with menstruation-associated TSS. First, it can occur in males, and TSS associated with infections not involving the vagina occurs equally in men and women. Of patients with non–menstruation-associated TSS, 11% were not white compared with only 2% of menstruation-associated TSS cases (13). The age range for non–menstruation-associated TSS ranged from the newborn to the elderly rather than the reproductive age span seen with menstruation-associated TSS.

Kain et al. (18) contrasted and compared the clinical and laboratory features of patients with NMTSS and those with MTSS. Compared to patients with MTSS, patients with NMTSS were a more heterogeneous group with varying host factors and clinical presentations. The NMTSS group differed from the MTSS group in terms of (i) frequency of prior antimicrobial therapy (46% vs. 16%; $p = 0.05$); (ii) rate of nosocomial acquisition (65% vs. 0%; $p = 0.0001$); and (iii) time of onset of fever and rash in relation to the initial symptoms ($p = 0.005$ and 0.03, respectively, with earlier onset in the NMTSS group). Patients with NMTSS experienced more frequent renal and central nervous system (CNS) complications and less frequent musculoskeletal involvement ($p = -0.07$ in all three). In this study, stepwise discriminant analysis identified four variables that differentiated NMTSS and MTSS patients: (i) delayed onset of TSS symptoms after the precipitating injury or event; (ii) more frequent CNS manifestations; (iii) less frequent musculoskeletal involvement; and (iv) higher degree of anemia. In addition, Kain et al. (18) reported that *S. aureus* associated with NMTSS and MTSS produced TSST-1 with comparable frequency (62% vs. 84%; $p = 0.2$). However, production of staphylococcal enterotoxin A was less common in NMTSS than MTSS (33% vs. 74%; $p = 0.01$), and MTSS strains more commonly coexpressed TSST-1 and staphylococcal enterotoxin A than did NMTSS isolates (68% vs. 28%; $p = 0.01$). Although mortality was higher in the NMTSS group (12.5% vs. 4.8%), this was not statistically significant. These authors concluded that NMTSS is clinically and microbiologically distinct from MTSS (18).

Prior to 1981, TSS occurring in adults was believed to be primarily a menstruation-associated syndrome related to tampon use. It now is recognized that TSS is associated with a wide variety of conditions unrelated to menses and/or tampon use (Table 11.1). In 1982, the CDC reported 54 cases of NMTSS (13). The

symptoms and signs in the cases were similar to those described in menstruation-associated TSS, and *S. aureus* was recovered from 88% of nonmenstrual cases. Nonmenstrual TSS has been reported in a variety of surgical procedures and soft tissue infection (Table 11.1). In a retrospective review of 390,000 surgical cases, Graham and coworkers (56) demonstrated that the incidence of postoperative TSS was 0.003% (12 cases). In addition, TSS has been reported in association with the use of contraceptive diaphragm (68,69 and 70) and vaginal contraceptive sponges (65). As noted by Friedell and Mercer (14), TSS can occur in almost any situation in which *S. aureus* infection can be harbored and an appropriate environment established to favor production of TSST-1. Disruption of normal skin or mucous membrane barrier that allows a localized *S. aureus* infection to transmit toxins systemically appears to be a common factor in nonmenstrual cases of TSS (14). MacDonald and coworkers (66) reported that TSS can occur as a complication of influenza and influenza-like illness. These authors identified nine cases compatible with TSS complicating influenza or influenza-like illness. *Staphylococcus aureus* was isolated from respiratory tract secretions in all eight cases cultured, and five of seven *S. aureus* isolates available for determination of exotoxin production produced TSST-1. Langmuir et al. (67) hypothesized that the plague of Athens, which ended the golden age of Athens, was TSS complicating an epidemic of influenza.

Surgical wound infections (13,14,57,58)
Soft tissue infections (3,14,59)
Cellulitis
Subcutaneous abscess
Osteomyelitis
Mastitis
Hidradenitis
Infected insect bite
Lung abscess
Bursitis
Purulent adenitis
Infected burns
Infected cutaneous ulcer
Postpartum cases (11–14,57,58,60–62)
Immediate neonatal period (60,61) (concomitant maternal TSS)
Female genital tract cases (9,10,13,58,63,64)
Vaginal infections
Acute salpingitis
Diaphragm use
Vaginal contraceptive sponge use (65)
Influenza (66,67)

TABLE 11.1. CONDITIONS ASSOCIATED WITH NONMENSTRUAL TOXIC SHOCK SYNDROME

Based on observations made in investigations demonstrating TSS associated with surgical wound infections (57,58), the incubation period for TSS ranged from 1 to 4 days (median 2 days). These data clearly demonstrate the potential for rapid development of a fulminant disease in previously healthy individuals who have been exposed to the specific factor(s) responsible for TSS (13).

Initial reports suggested that the case fatality rate for TSS was as high as 13% (4,9). The three major causes of death in TSS are adult respiratory distress syndrome (ARDS), intractable hypotension, and hemorrhage due to disseminated intravascular coagulation (DIC). Subsequent reports noted a dramatic decrease in the case fatality rate for TSS, with a rate of 3.1% in 1981 (45) and no deaths associated with MTSS in 1988 and 1989 (6). At the present time, mortality from staphylococcal TSS usually

is less than 5% (2). This improvement in survival most likely is a reflection of increased awareness of TSS by clinicians, with resultant early diagnosis and institution of appropriate therapeutic measures.

A recurrence rate of approximately 30% was noted by investigators at the CDC (4,8). Multiple recurrences have been reported in the same patient (6,8,63). Kain et al. (18) reported that the recurrence rate was similar for patients with MTSS and NMTSS. In both instances, recurrence was significantly more frequent in the absence of specific antistaphylococcal therapy.

Streptococcal Toxic Shock Syndrome

In the last half of the 1980s, there was a reemergence of rheumatic fever and severe group A streptococcal infections in developed countries (1). Fulminant group A streptococcal infections associated with shock, organ failure, necrotizing fasciitis, bacteremia, and death occurred and were termed streptococcal toxic shock syndrome (1,2). In 1987, Cone et al. (23) reported two cases of severe group A streptococcal infection that had clinical features similar to staphylococcal TSS. Bartter et al. (25) applied the name toxic streptococcal syndrome or streptococcal toxic shock-like syndrome to this entity.

Stevens et al. (26) further characterized the syndrome in a series of 20 patients. Patients were generally healthy and less than 50 years of age. All had invasive group A streptococcal infection associated with shock, multiorgan system involvement, and rapidly progressive destructive soft tissue infection (e.g., necrotizing fasciitis). The case fatality rate was 30% despite appropriate treatment. Among the isolates available for testing, M types 1 and 3 were the most common serotypes, and 80% produced pyrogenic exotoxin A (26). By 1995, Stevens (71) summarized more than 100 additional published reports of cases of streptococcal TSS. Cases of streptococcal TSS tend to be sporadic, with an estimated prevalence of 10 to 20 cases per 100,000 population at the maximum (1).

Eriksson et al. (35) assessed the epidemiologic and clinical aspects of streptococcal TSS. In their retrospective review of group A streptococcus invasive infections in Stockholm from 1987 to 1995, they noted an incidence of 2.3 (annual range 1.3 to 3.7) cases per 100,000 residents. The incidence increased with age, being 6.1 per 100,000 individuals over 65 years of age. Streptococcal TSS developed in 19 (13%) of the 151 episodes of invasive group A streptococcal infection. The case fatality rate was 11% overall, but among the cases of streptococcal TSS the fatality rate was 47%. In a multivariate logistic regression model, streptococcal TSS was significantly associated with alcohol abuse (odds ratio [OR], 6.3) and infection with a M1T1 strain (OR, 6.7). Case fatality was associated with age (OR, 14.5), immunosuppression (OR, 4.7), and streptococcal TSS (OR, 21.5). Hypotension was significantly associated with mortality, whether or not TSS developed.

Among obstetric and gynecologic patients, streptococcal TSS has occurred with cellulitis, wound infection, septic abortion, postpartum endomyometritis, and peritonitis (26,29,30,71). Although streptococcal TSS in obstetrics and gynecology is seen most often in pregnant patients, this entity has occurred with after vaginal and abdominal hysterectomy infections, ovarian abscesses, and pelvic inflammatory

disease, with or without an intrauterine device (26,72,73 and 74).

Clostridium Sordellii Toxic Shock Syndrome

Since the 1980s, there have been six obstetric cases of *C. sordellii* TSS documented in the literature (40,41,42,43 and 44). These cases of necrotizing subcutaneous and muscle infections with *C. sordellii* occurred in obstetric patients following vaginal or cesarean deliveries (44). In contrast to other clostridial soft tissue infections characterized by widespread undermining of the subcutaneous tissue, myonecrosis, and rapid progression of tissue destruction away from the wound site, puerperal *C. sordellii* infections present with relatively "clean" incisions and localized tissue damage (44). Rather, *C. sordellii* is associated with a profound exotoxin-mediated systemic response characterized by anasarca, refractory hypotension, and marked leukocytosis (44). None of the obstetric patients with *C. sordellii* TSS survived (40,41,42,43 and 44).

ETIOLOGY

Staphylococcal Toxic Shock Syndrome

A significant association between TSS and tampon use was identified in a series of case-control epidemiologic studies (4,5,7,8,75,76 and 77). Nearly 70% of women in the United States used tampons during their menstrual period; a significantly greater proportion used tampons during the menstrual period in which TSS occurred than did matched controls.

Initial studies revealed no association between TSS and any specific brand of tampons (4,5,7,8). However, subsequent investigations demonstrated a significant association between TSS and the use of Rely® tampons (46,48,75,76 and 77). In September 1980, the CDC reported that 26% of controls used Rely® tampons, but 71% of TSS cases were exclusive Rely® users (46). Schlech and coworkers (76) reported that the relative risk for development of TSS among Rely® users compared with users of other tampon brands was 7.7 (99% confidence interval [CI], 2.1 to 27.9). These workers noted no significant influence of tampon absorbency that could be separated from the risk associated with the use of Rely®. Osterholm and associates (77) demonstrated that the odds ratio for developing menstruation-associated TSS with any use of tampons compared with no use of tampons was 18 ($p < 0.001$). When exclusive use of particular tampon brands was evaluated, Rely® was the only brand with a significantly increased odds ratio (2.49; $p = 0.005$). This increased relative risk with Rely® tampons was beyond that predicted by absorbency alone. In contradistinction to the CDC findings (76), Osterholm et al. (77) demonstrated that women who used high-absorbency tampons had a greater relative risk of developing TSS than women who used low-absorbency tampons. Clearly, tampon use has been established as a risk factor for TSS in menstruating women, with an odds ratio ranging from 11 to 18 in the initial studies conducted in 1980 (7,8,51,76,77). Based on cases in 1983 and 1984, Berkley et al. (54) reported an odds ratio of 33 for tampon use versus no tampon use. In the 1980 studies designed to assess the role of specific tampon brands, the odds ratio for the use of Rely® tampons compared with the use of other brands ranged from 2.5 to 7.7 (51,76,77 and 78). The results of the 1983–1984 study (54) and the data from the

1980 CDC II study are compared in Table 11.2. The risk for Rely® tampons was substantially higher than for other brands. The brands available during both intervals had similar odds ratios.

	Results in Indicated Study	
Brand	CDC II[a]	CDC III[b]
Tampax	1.0	1.0
OB	1.4	1.1
Kotex	1.5	1.7
Playtex	3.0	3.1
Rely	13.2	—

[a]Conducted July 1980 to August 1980
[b]Conducted January 1983 to December 1984
CDC, Centers for Disease Control and Prevention.
From Broome CV. Epidemiology of toxic shock syndrome in the United States: overview. *Rev Infect Dis* 1989;11[Suppl 1]:514–521, with permission.

TABLE 11.2. RISK OF TOXIC SHOCK SYNDROME IN SINGLE-BRAND USERS COMPARED WITH THAT IN REFERENCE USERS OF TAMPAX TAMPONS

Several mechanisms by which tampons increase the risk of TSS have been suggested. In the tristate study in 1980, a significant increase in risk with tampons of higher absorbency was found, and the authors raised a question whether the chemical composition of tampons might be a factor in the development of TSS (77). To assess the interaction of absorbency and chemical composition, Berkley et al. (54) (CDC study III) compared tampon brands used by women with MTSS reported to the CDC passive surveillance system in 1983 and 1984 with those used by women in a national marketing survey during the same time period. The results clearly demonstrated an increased risk with the use of tampons with increased absorbency (Fig. 11.2). For each 1-g increase in absorbency, the risk of TSS increased by 37% (OR, 1.37; 95% CI, 1.29–1.45). Although absorbency has been evaluated because it is readily quantifiable and standardized measurements are available, as noted by Broome (17), absorbency may be a surrogate for some other dose-response effect, such as increased oxygen content or increased ability to bind cations such as magnesium.

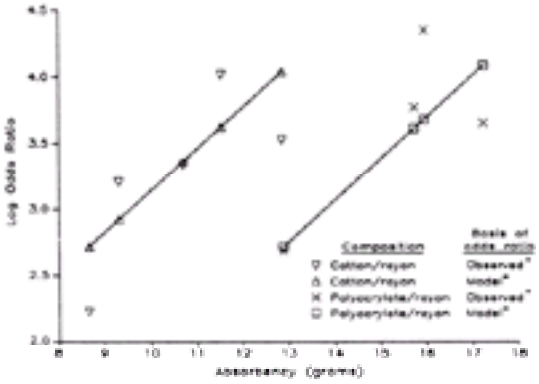


FIGURE 11.2. Odds ratios for toxic shock syndrome based on tampon absorbency and chemical composition. *Adjusted for age group and year of survey.

Toxic shock syndrome occurs in nonmenstruating females and in men. Thus, it is apparent that tampons by themselves are not the explanation for TSS. However, the composition of materials used in tampons may play an important role in the development of TSS (47). As noted by Shands et al. (8), prior to 1977, all tampon products were made of rayon or a rayon/cotton blend. After 1977, 44% of tampon products with 65% of the market contained more absorbent synthetic materials, such as polyacrylate fibers, carboxymethylcellulose, high-absorbency rayon-cellulose, and polyester foams. Tierno (79) and Hanna (80) have postulated that these synthetic components interact with the bacterial flora of the vagina to provide an environment that is appropriate for the growth of toxin-producing staphylococci. However, most observers were of the opinion that the increased risk associated with the higher-absorbency tampons appeared to be independent of tampon composition (77,81). Subsequently, Tierno and Hanna (82) reported that cotton tampons lead to little, if any, TSST-1 production by *S. aureus* and that cotton absorbed any toxin that was produced. These authors concluded that tampons made solely of cotton would be safer than the cotton/rayon tampons currently available in the United States. These data, which are inconsistent with the epidemiologic data demonstrating that the risk of TSS is mainly dependent on tampon absorbency rather than composition, have been questioned and refuted by Schlievert (83) and Parsonnet et al. (84). Schlievert (83) demonstrated that cotton tampons neither prevent TSST-1 production nor significantly absorb toxin onto the fibers. Parsonnet et al. (84) noted that neither cotton nor rayon tampons consistently increased toxin production, nor were there significant differences between them or their effects on TSST-1. On the other hand, tampons composed of carboxymethylcellulose and polyester foam increased TSST-1 production (84).

The association of TSS with *S. aureus* was identified in the original case-control studies (7,8). Davis et al. (7) reported that *S. aureus* was recovered in 17 of 23 cervicovaginal cultures obtained from TSS patients. Similarly, Shands and coworkers (8) recovered *S. aureus* from 62 of 64 vaginal cultures from women with menstruation-associated TSS. Among TSS cases reported to the CDC as of October 1982, *S. aureus* was recovered from 210 of 215 patients (45). Crass and Bergdoll (85) studied cultures of *S. aureus* from 434 individuals with TSS. Over 90% of these isolates produced TSST-1. Isolates producing both staphylococcal enterotoxin C and TSST-1 had a greater association with nonmenstrual and fatal cases. *Staphylococcus aureus* may be present as part of the normal bacterial flora of the vagina and cervix in healthy women. It has been recovered from 0% to 15% of vaginal specimens (6,86,87,88,89,90 and 91), with 5% to 10% the generally accepted prevalence. Interestingly, several studies have noted an increase in the incidence of *S. aureus* colonization of the female lower genital tract at the time of menses (92,93). Noble et al. (93) reported the recovery of *S. aureus* from 17% of their patients during menstruation compared with 5.8% at mid cycle in the same women. Saunders and associates (94) suggested that an imbalance among the normal microflora of the female genital tract may be crucial to the development of menstruation-associated TSS. They reported that lactobacilli, which play a major role in maintaining the

normal vaginal environment, have an inverse relationship with staphylococci, and they postulated that lactobacilli served as a natural defense against *S. aureus.* Moreover, they suggested that an increase in *S. aureus* may occur because tampons (especially superabsorbable types) remove substrates necessary for lactobacilli to exert this inhibitory effect.

The abrupt onset of the clinical presentation, the multisystem involvement, the rarity of bacteremia, and the similarity of TSS to other illnesses known to be caused by bacterial toxins led investigators to hypothesize that a toxin, either alone or synergistically with another factor(s), was responsible for TSS. With the demonstration that *S. aureus* was recovered from nearly 100% of TSS cases, speculation focused on a staphylococcal toxin as the culprit.

Investigations quickly focused on identification of the presence of staphylococcal toxins associated with isolates of *S. aureus* recovered from patients with TSS (48,95,96). Schlievert (95) identified a protein that he named pyrogenic exotoxin C. In this investigation, pyrogenic exotoxin C was present in 28 of 28 *S. aureus* recovered from TSS cases but in only five (16%) of 32 *S. aureus* recovered from controls. Altemeier et al. (96) found pyrogenic exotoxin C was produced by 131 (91%) of 144 TSS isolates of *S. aureus.* Bergdoll and associates (97) simultaneously identified a toxin with similar physical characteristics, which they called enterotoxin F. They reported that 61 (94%) of 65 *S. aureus* strains from TSS patients produced enterotoxin F, and only four (4.6%) of 87 non-TSS *S. aureus* strains produced enterotoxin F. Furthermore, in a prospective blinded study, Bergdoll et al. (97) noted that all 34 *S. aureus* strains from TSS produced enterotoxin F compared with three (11%) of 26 control strains. In the early 1980s, a consensus developed that pyrogenic exotoxin C and staphylococcal enterotoxin F were identical (98,99).

Subsequent work has demonstrated that these two toxins are coded by the same gene in the staphylococcal chromosome and thus are identical (100). The current name for this toxin is toxic shock syndrome toxin 1 (TSST-1) (101). Studies in baboons have shown that TSST-1 produces many of the clinical and laboratory manifestations of TSS (102). As described by Crass and Bergdoll (85), this toxin has been demonstrated to be a potent inducer for production of interleukin-1 (IL-1) by macrophages, is a nonspecific T-cell mitogen, and induces suppression of some immune responses.

Schlievert (103) has demonstrated that TSST-1 significantly enhanced susceptibility to lethal endotoxin shock by 50,000-fold. Larsen and Schlievert (99) suggested that this enhancement of endotoxin may explain the manifestations of Gram-negative septic shock associated with TSS, and that the combination of TSST-1 and small amounts of circulating endogenous endotoxin from the normal bowel flora provides the best explanation for the pathogenesis of TSS. The massive release of IL-1 has been implicated in mediating many of the symptoms of TSS (104). Toxic shock syndrome toxin 1 is a potent stimulator of IL-1 release (104,105). Beezhold et al. (106) reported that TSST-1 is a more potent inducer of IL-1 than endotoxin, and a synergistic induction of IL-1 was observed when macrophages were stimulated with both TSST-1 and endotoxin. Toxic shock syndrome toxin 1 has been shown to stimulate production of tumor necrosis factor alpha (TNF-a) (107). Similarly, other TSS-associated exotoxins and endotoxins induce TNF production (108).

These findings are explained by the concept of superantigens, which are a class of

bacterially and virally encoded proteins that stimulate a massive immune response by their ability to bypass processing by antigen-processing cells and to bind directly with Class II major histocompatibility molecules, thus stimulating massive numbers of T cells (110). Toxic shock syndrome toxin 1 is such a superantigen. Nearly all MTSS is caused by TSST-1–producing *S. aureus* (110). Toxic shock syndrome toxin 1 accounts for half of NMTSS cases; staphylococcal enterotoxins B and, to a lesser extent, C account for the remainder (110).

Bergdoll and coworkers (97) demonstrated that immunologic status, vis-à-vis TSST-1, may be important in the pathogenesis of TSS. They found that TSS patients had a greater serosusceptibility to enterotoxin F (TSST-1) than did controls; anti-staphylococcal enterotoxin F antibody was present in titers ³1:00 in five (17.2%) of 29 TSS patients, compared with 44 (78.6%) of 56 controls. Crass and Bergdoll (85) tested the sera of 284 patients with TSS for antibodies to TSST-1. They reported that 82.4% of sera from TSS patients had no detectable level of antibody, whereas nearly 80% of healthy controls had antibody levels ³1:800. In this study, the sera from TSS patients also had lower levels of antibody to staphylococcal enterotoxins A, B, and C than did the controls. These authors noted that their findings indicate that TSS patients may have an immunodeficiency that inhibits production of and/or maintenance of antibodies to TSST-1 and staphylococcal enterotoxins.

Several variables that influence toxin production have been described (22). These include increased oxygen, increased carbon dioxide, temperature elevation, and a high pH. Wagner et al. (111) noted that insertion of tampons changes the internal vaginal milieu from an anaerobic to an aerobic state. This increase in oxygen tension enhances the growth of, and toxin production by, *S. aureus*.

Mills et al. (112) suggested that magnesium ion controls the production of TSST-1. With lowered concentrations of Mg^{2+}, toxin production was increased significantly. Conversely, with higher concentrations of Mg^{2+}, the production of TSST-1 was suppressed. There is a direct correlation between absorbency and binding of magnesium, with the most absorptive fibers having the greatest capacity to bind Mg^{2+}. Thus, high-absorbency tampons are associated with low levels of Mg^{2+} and consequent high production of TSST-1 (22). Kass and Parsonnet (22) claim that absorbability and magnesium-binding capacity can be separated and that the magnesium-combining capacity is critical to the production of TSST-1. Kiyota et al. (113) reported that magnesium-deficient strains of *S. aureus* secrete more exoprotein than under conditions when magnesium is not limiting. Multiple studies have demonstrated that the concentration of magnesium ion controls the production of TSST-1 and other exoproteins secreted by strains of *S. aureus* (22,112,113,114 and 115).

Duff (55) noted that three conditions are required for development of TSS. First, the patient must be colonized or infected with *S. aureus*. Second, the staphylococci must be capable of producing the toxin(s) that is associated with the clinical manifestations of TSS. Third, there must be a portal for the toxin(s) to enter the systemic circulation. In NMTSS, *S. aureus* is present in a localized supportive infection; as toxin is produced, it is absorbed from the infected site into the bloodstream. Duff (55) suggested several mechanisms by which staphylococcal toxin gains access to the systemic circulation in menstruation-associated TSS. Toxin could be absorbed through microulcerations in the vaginal mucosa secondary to trauma from tampons

and/or inserters. Superabsorbable tampons may obstruct menstrual flow, producing reflux of menstrual blood containing toxin through the fallopian tubes into the peritoneal cavity. This would result in absorption of toxin across the peritoneum. Alternately, toxin could be absorbed across the denuded endometrial surface.

Streptococcal Toxic Shock Syndrome

Following World War II, the rates of morbidity and mortality due to group A streptococcal infections declined steadily (36). Since the mid-1980s, a resurgence of severe, invasive disease has occurred (1,2,23,24,25,26,27,28,29,30,31,32 and 33,35,36,116). The most severe form of invasive group A streptococcal infection was recognized as streptococcal TSS (32). The increased incidence of invasive group A streptococcal infections has been associated with an increase in virulence and severity, with many cases of streptococcal TSS and necrotizing fasciitis (117,118 and 119). Whether this change in epidemiology and clinical manifestations is due to the acquisition of new virulence by the organism or compromised host susceptibility to virulence factors produced by the organism remains uncertain (36).

Group A streptococci produce multiple virulence factors that contribute to the pathogenesis of invasive group A streptococcal disease (36). These include surface M protein, hyaluronic capsule, proteases, DNases, lipoteichoic acid, streptolysins O and S, and pyrogenic exotoxins (36). Most importantly, the streptococcal pyrogenic exotoxins function as superantigens that result in activation of large numbers of immune cells. This, in turn, leads to the synthesis and release of very large amounts of inflammatory cytokines that mediate many of the systemic manifestations of sepsis, including hypotension and multiorgan failure (120,121).

Group A streptococci produce three pyrogenic exotoxins: streptococcal pyrogenic exotoxins A, B, and C (1). These exotoxins induce fever and facilitate development of shock by lowering the threshold to endotoxin (1,110). Streptococcal pyrogenic exotoxins A and B induce mononuclear cells to produce inflammatory cytokines, including TNF-g, IL-1b, and interleukin-6 (122,123). These inflammatory cytokines mediate the fever, hypotension, organ failure, and tissue injury associated with streptococcal TSS (36). Two recently identified pyrogenic exotoxins, streptococcal superantigen and mitogenic factor, also can induce a cytokine synthesis, but their role in streptococcal TSS has not been elucidated (36).

Lack of protective immunity against the virulence factors produced by group A streptococci may increase host susceptibility to infection (36). Initial studies suggested that low levels of antibodies against specific streptococcal pyrogenic exotoxins or the M protein increase host susceptibility to invasive group A streptococcal infection (124,125). As a result, it was hypothesized that the low levels of anti-M1 antibody in the general populations may have contributed to the reemergence of severe group A streptococcal infections in the United States, Canada, and Scandanavia (124,125 and 126). However, Basma et al. (36) failed to confirm this hypothesis. These investigators studied 33 patients with invasive infection caused by genotypically indistinguishable M1T1 strains of *S. pyogenes* who had different disease outcomes. Although levels of anti-M1 antibodies and antistreptococcal superantigen antibodies were significantly lower in severe (with hypotension) and nonsevere (without hypotension) invasive group A streptococcal infection than in age-matched and geographically matched healthy controls, the levels of these protective antibodies from severe and nonsevere cases were not

different (36). Basma et al. (36) concluded that low levels of protective antibodies may contribute to host susceptibility to invasive streptococcal infection but do not modulate disease outcome.

Clostridium Sordellii Toxic Shock Syndrome

Clostridium sordellii is one of the histotoxic clostridium species that has been associated (usually with other organisms) with production of gas gangrene. There have been descriptions of a distinct TSS attributed to soft tissue infection with *C. sordellii* alone (37,38,39,40,41,42,43 and 44). Since 1929, it has been recognized that the virulence of *C. sordellii* was due to a toxin (beta toxin) that caused severe, gelatinous edema in animal models (127). Subsequently, beta toxin was divided into an edema-producing or lethal toxin and a hemorrhagic toxin (128). The lethal toxin is primarily responsible for the morbidity and mortality associated with *C. sordellii* infection (44).

The natural reservoir for *C. sordellii* is the gastrointestinal and genital tract. Sosolik et al. (44) reviewed the pathogenesis of *C. sordellii* TSS. Following damage to the mucosa, skin, and other natural barriers associated with cesarean delivery or episiotomy with vaginal delivery, an anaerobic environment is created secondary to decreased local blood flow and proliferation of indigenous flora. If a toxin-secreting strain of *C. sordellii* is present and proliferates, tissue necrosis and production of lethal toxin and hemorrhagic toxin occur. Rapid dissemination of the toxins, especially lethal toxin, occurs, leading to the morbidity and mortality associated with *C. sordellii* TSS.

CLINICAL PRESENTATION

Staphylococcal Toxic Shock Syndrome

Toxic shock syndrome is a multisystem disease with a wide range of symptoms, signs, and laboratory findings. Characteristically, TSS occurs abruptly with the sudden onset of high fever, chills, myalgias, vomiting, diarrhea, hypotension, and generalized “sunburn-like” rash. The case definition proposed by the CDC is given in Table 11.3.

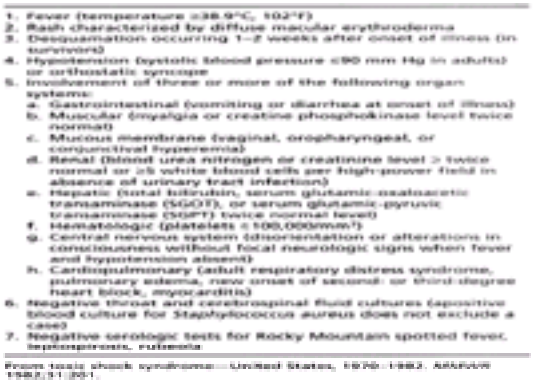


TABLE 11.3. CASE DEFINITION OF TOXIC SHOCK SYNDROME

The most commonly observed clinical signs and symptoms of TSS are given in Table 11.4. Involvement of the skin and mucous membranes is one of the most characteristic findings. The rash, which occurs early in the disease process, presents as a “sunburn-like” macular erythema; it can evolve to where the patient appears like a “broiled lobster.” Five to 12 days after the onset of TSS in surviving patients, a fine desquamation occurs on the face, trunk, and extremities. This is followed by the nearly pathognomonic full-thickness, peeling-like desquamation of the palms and/or soles. The staphylococcal toxin(s) has a predilection for mucous membranes, and their involvement is often a prominent feature of TSS (47). This manifests clinically as sore throat, oropharyngeal hyperemia, strawberry tongue, nonpurulent conjunctivitis, and/or vaginal hyperemia.

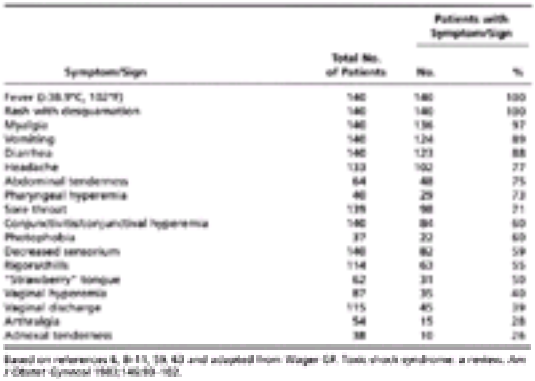


TABLE 11.4. CLINICAL SIGNS AND SYMPTOMS COMMONLY SEEN IN PATIENTS WITH TOXIC SHOCK SYNDROME

Gastrointestinal symptoms and signs are frequent and prominent in TSS. Vomiting and watery diarrhea have been noted in approximately 90% of cases. These symptoms occur early in the disease, usually are severe, and are associated with marked generalized abdominal tenderness. Hepatomegaly and pancreatitis have been reported occasionally.

Another early characteristic finding is the presence of myalgias, which have been reported in 88% to 100% of TSS cases (6,9,10 and 11,59). Exquisite muscle tenderness can be elicited by movement or touch. Additional musculoskeletal findings include arthralgias, synovitis of hand joints, and sterile joint effusions.

Neurologic involvement may be difficult to assess in the presence of high fever and/or severe hypotension associated with TSS. In general, neurologic symptoms and signs have included headache, confusion, loss of consciousness, disorientation, agitation, photophobia, seizures, meningeal irritation, and evidence of psychomotor retardation. Tofte and Williams (9) and Chesney et al. (11) noted normal glucose and protein levels and very low counts of mononuclear or polymorphonuclear cells in the

spinal fluid.

Hypotension and shock are prominent features of TSS. They occur early in the disease process and constitute one of the major criteria for the diagnosis of TSS. The presence of orthostatic syncope now has been accepted as an alternative criterion for documented shock. Multiple cardiac abnormalities have been reported in TSS cases. These include sinus or supraventricular tachycardia, first-degree heart block, premature ventricular beats, nonspecific ST-T wave changes, and T-wave inversion in precardial leads (6,9,11,47,59). Shands et al. (8) reported cases with pericarditis and vasculitis. Chesney and coworkers (11) noted that low central venous pressure was present in their TSS cases. McKenna and associates (6), using Swan-Ganz measurements, noted that TSS patients had high cardiac output, low peripheral resistance, normal pulmonary wedge pressure, and normal pulmonary resistance.

Renal involvement has been demonstrated in more than 80% of patients with TSS (6,8,9,10 and 11,59). This renal dysfunction has been manifested by sterile pyuria, mild proteinuria, hematuria, azotemia, hyponatremia, increased urinary sodium, hyperkalemia, and decreased creatinine clearance.

The prognosis for patients with TSS often is determined by the presence of pulmonary involvement, especially ARDS or “shock lung.” Fisher and coworkers (10) reported that tachypnea and hypoxemia (Po_2 <60 mm Hg) were seen frequently in TSS patients. Radiologic evidence of pulmonary edema and/or pleural effusions has been reported (10,11). Progression of these respiratory findings to ARDS in TSS patients is well documented (6,8,9,10 and 11,59). Most likely, ARDS occurs as a consequence of the enhanced activity of endotoxin caused by TSST-1 (103). Once ARDS develops, the prognosis is poor, especially when extensive or prolonged ARDS is present (47).

The laboratory abnormalities reported in TSS cases reflect the multisystem involvement characteristic of the disease. A summary of the more frequent laboratory findings is given in Table 11.5. Some of the more commonly reported metabolic and electrolyte abnormalities include metabolic acidosis, hypocalcemia, hypokalemia, hyponatremia, and hypophosphatemia. Hypercalcitoninemia has been suggested as the cause of the low calcium levels characteristically associated with TSS (129). Among the frequent hematologic abnormalities are anemia, thrombocytopenia, leukocytosis, prolonged prothrombin time, increased prolonged partial thromboplastin time, and increased fibrin degradation products. Hepatic involvement is manifested by increased liver enzymes and hyperbilirubinemia. Renal involvement is signaled by the occurrence of azotemia, increased serum creatinine, pyuria, hematuria, and proteinuria. In addition, increased creatine phosphokinase connotes muscle involvement.

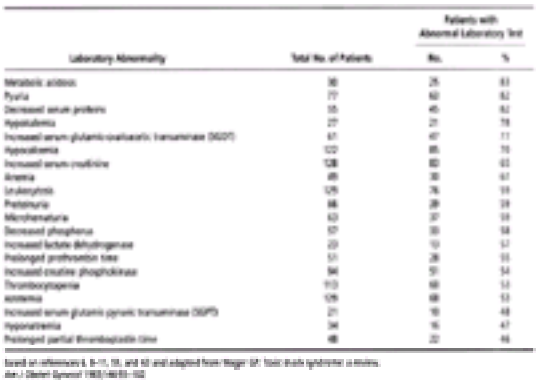


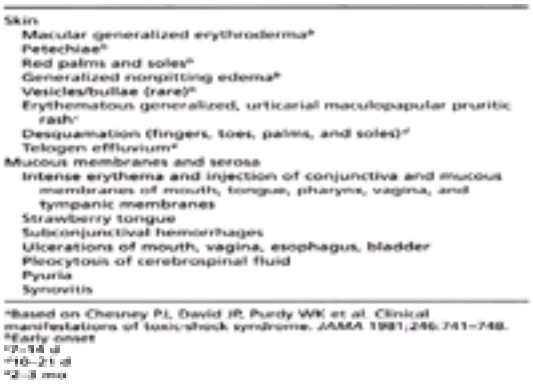
TABLE 11.5. LABORATORY ABNORMALITIES COMMONLY SEEN IN PATIENTS WITH TOXIC SHOCK SYNDROME

Chesney et al. (11) extensively reviewed the clinical aspects and spectrum of illness in TSS. According to their review, among the distinctive pathophysiologic aspects of TSS are (i) the rapidity with which clinical manifestations can present and progress in a previously health individual; (ii) the rapid onset of hypotension secondary to decreased vasomotor tone and nonhydrostatic leakage of fluid to the interstitial space resulting in tissue ischemia and multisystem organ failure (Table 11.6); (iii) the presence of multisystem organ involvement due to direct action of toxin and/or mediators on cells and poor tissue perfusion; (iv) the spectrum of involvement of skin and mucous membranes (Table 11.7); and (v) the high rate of recurrence in patients with untreated TSS (11).

Increased	Decreased
Capillary leakage of fluid into interstitial space	Systemic vascular resistance
	Intravascular volume
	Tissue perfusion
Generalized nonpitting edema	Central venous pressure
Cardiac index	Blood pressure
	Pulmonary artery wedge pressure

From Chesney PJ, David JP, Purdy WK, et al. Clinical manifestations of toxic-shock syndrome. JAMA 1981;246:741–748.

TABLE 11.6. EARLY HEMODYNAMIC CHANGES IN TOXIC SHOCK SYNDROME



Skin
Macular generalized erythroderma[a]
Petechiae[b]
Red palms and soles[b]
Generalized nonpitting edema[a]
Vesicles/bullae (rare)[b]
Erythematous generalized, urticarial maculopapular pruritic rash[c]
Desquamation (fingers, toes, palms, and soles)[c]
Telogen effluvium[c]
Mucous membranes and serosa
Intense erythema and injection of conjunctiva and mucous membranes of mouth, tongue, pharynx, vagina, and tympanic membranes
Strawberry tongue
Subconjunctival hemorrhages
Ulcerations of mouth, vagina, esophagus, bladder
Pleocytosis of cerebrospinal fluid
Pyuria
Synovitis

[a]Based on Chesney PJ, David JR, Purdy WK et al. Clinical manifestations of toxic shock syndrome. JAMA 1981;246:741–748.
[b]Early onset
[c]7–14 d
[d]10–21 d
[e]2–3 mo

TABLE 11.7. SPECTRUM OF SKIN AND MUCOUS MEMBRANE INVOLVEMENT IN TOXIC SHOCK SYNDROME[a]

Despite the severe clinical manifestations of TSS, the vast majority of patients recover without residual effects. Chesney and colleagues (11) arbitrarily divided the sequelae associated with TSS into two groups. The late-onset findings occur between days 4 and 14 of the acute illness. This group includes the desquamation of skin and peeling of palms and/or soles; impaired sensation of the fingers; swollen, denuded tongue; transient vocal cord paralysis; acute tubular necrosis with renal failure; ARDS; and, most recently, carpal tunnel syndrome (130). The second group of late findings occurs 60 or more days after onset of the TSS episode. Included in this group are splitting of the nails, reversible loss of hair and nails, CNS sequelae, renal impairment, cardiac dysfunction, and, as suggested by Wager (47), recurrent episodes of TSS.

Of particular concern is the report by Rosene and coworkers (131) demonstrating persistent neurologic sequelae in survivors of TSS. These investigators studied 12 women 2 to 12 months after recovery from TSS episodes. They reported that six had demonstrable abnormalities in intellectual function, such as impaired memory, concentration, and ability to perform mathematical calculations. All 12 women had hyperreflexia at follow-up. In addition, eight had abnormal electroencephalograms, and five had disturbances in cerebellar function. In a follow-up evaluation of 36 TSS patients, Chesney et al. (132) noted a frequent incidence of late sequelae. Three patients were found to have prolonged neuromuscular dysfunction, one with vocal cord paralysis and two with diffuse myopathy. One patient with acute renal failure secondary to acute tubular necrosis during her acute episode of TSS had markedly impaired creatinine clearance 9 years later. In addition, they reported that one patient had persistent cyanosis of her feet and hands 9 months after the initial TSS episode.

It has been well documented that TSS can recur, especially in women with menstruation-associated disease. Recurrence rates from 28% to 64% were reported in the initial studies identifying TSS (6,7 and 8), with a recurrence rate of approximately 33% being the general consensus. Davis et al. (7) noted that recurrences were significantly less frequent in patients who received b-lactamase–resistant, antistaphylococcal antibiotics during their initial episode of TSS. Kain et al. (18) reported that recurrences occurred in both NMTSS and MTSS and that recurrences were more frequent in both groups in the absence of specific

antistaphylococcal therapy.

Because of confusion regarding what constitutes a recurrent episode of TSS, three categories based on the presence or absence of the major criteria for diagnosis of TSS have been proposed. These recurrence categories for TSS are given in Table 11.8.

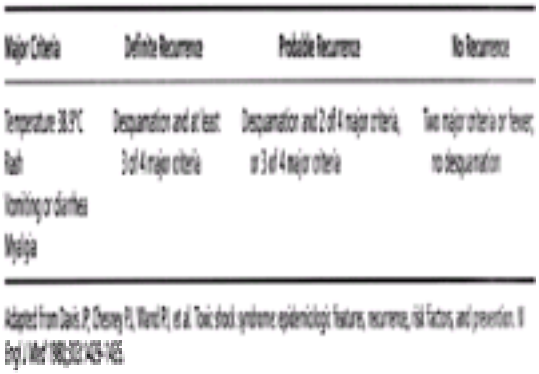


TABLE 11.8. RECURRENCE CATEGORIES FOR TOXIC SHOCK SYNDROME

Toxic shock syndrome associated with surgical wound infections generally presents as an early-onset wound infection within 48 hours postoperatively. Unlike other early-onset wound infections caused by *Clostridia perfringens* or group A b-hemolytic streptococci, TSS-associated wound infections have minimal or absent local signs of infection such as erythema, fluctuance, or drainage (57,58). However, *S. aureus* is nearly always recovered from these benign-appearing wounds. As noted by Bartlett and coworkers (58), the key clinical point is the occurrence of watery diarrhea and diffuse erythroderma in association with high fever in the initial several days postoperatively. Such findings, especially if hypotension is coexistent, must result in prompt evaluation of the operative wound for evidence of *S. aureus* infection.

Tofte and Williams (63) have suggested that TSS is associated with a broad spectrum of clinical manifestations and that many cases do not fulfill the strict epidemiologic criteria defined by the CDC (45), are generally milder, and do not present with life-threatening hypotension. As a result, these researchers proposed a case definition of “probable TSS.” These criteria are given in Table 11.9. It is important for clinicians to recognize these milder cases of TSS in order to institute early and appropriate therapy. These milder “probable TSS” cases may subsequently develop into the severe, life-threatening form of TSS. In the past, we admitted two such patients with severe, classic TSS who had presented to the emergency room several days previously with, in retrospect, mild symptoms and signs of TSS. One case occurred with a vaginal contraceptive sponge and the second was in association with a perirectal abscess.

≥3 criteria and desquamation or ≥5 criteria without desquamation
Criteria
Temperature ≥38°C, 102°F
Rash
Hypotension, orthostatic dizziness, or syncope
Myalgia
Vomiting, diarrhea, or both
Mucous membrane inflammation (conjunctivitis, pharyngitis, vaginitis)
Clinical abnormalities of ≥2 organ systems
Reasonable evidence for absence of other etiologies

From Dornan KJ, Thompson DM, Conn AR, et al. Toxic shock syndrome in the postoperative patient. *Surg Gynecol Obstet* 1982;154:65–68.

TABLE 11.9. DIAGNOSTIC CRITERIA OF PROBABLE TOXIC SHOCK SYNDROME

Streptococcal Toxic Shock Syndrome

A wide variety of group A streptococcal infections may result in streptococcal TSS (1). Although some patients with group A streptococcal infection develop shock or death late in the disease course, the case definition of streptococcal TSS requires that shock and organ failure occur early in the course of infection (32,133). According to Stevens (1), streptococcal TSS is defined as any group A streptococcal infection accompanied by early onset of shock and organ failure. The case definitions for definite and probable cases of streptococcal TSS are given in Table 11.10. Many sites of infection are associated with development of streptococcal TSS, including necrotizing fasciitis, cellulitis, erysipelas, myonecrosis, sinusitis, pharyngitis (rare), epiglottitis, pneumonia, peritonitis, genital tract infection, meningitis, and septic joint (1,71). Eriksson et al. (35), in a review of 151 invasive group A streptococcal infections in Sweden, noted that skin and soft tissue (e.g., cellulitis, erysipelas) were the most frequent clinical focuses of infection (80 [53%] cases). The next most frequent was no identified site of infection, with 39 (26%) cases (35). The clinical presentation commonly associated with streptococcal TSS was deep tissue infection (e.g., pneumonia, peritonitis, or necrotizing fasciitis) (1). However, infection without an identified focus also was commonly associated with streptococcal TSS (8/39 [21%]) (35).

I. Isolation of group A streptococci (*Streptococcus pyogenes*) A. From a normally sterile site (e.g., blood, cerebrospinal, pleural, or peritoneal fluid; tissue biopsy; surgical wound) B. From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion)
II. Clinical signs of severity A. Hypotension: systolic BP ≤90 mm Hg in adults or less than fifth percentile for age in children and B. ≥2 of the following signs: 1. Renal impairment: creatinine ≥177 uM (≥2 mg/dL) 2. Coagulopathy: <100 × 10^9/L (<100,000/mm³) or disseminated intravascular coagulation (prolonged clotting time, low fibrinogen levels, and presence of fibrin degradation products) 3. Liver involvement: serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), or total bilirubin twice or greater than upper limits of normal 4. Adult respiratory distress syndrome 5. Generalized erythematous macular rash that may desquamate 6. Soft tissue necrosis (necrotizing fasciitis, myositis, or gangrene)

[a]An illness fulfilling criteria IA and II (IA and B) are defined as a definite case. An illness fulfilling criteria III and II (A and B) are defined as a probable case if no other etiology for the illness is identified.

TABLE 11.10. PROPOSED CASE DEFINITION FOR STREPTOCOCCAL TOXIC SHOCK SYNDROME[a]

Streptococcal TSS often begins insidiously (1,2). Nearly 20% of patients experience a flu-like syndrome characterized by fever, pain, chills, myalgias, pharyngitis, nausea, vomiting, and diarrhea (125,134). Some cases present initially with fever and gastrointestinal symptoms prior to overdevelopment of streptococcal TSS (1). Pain tends to be the most common symptom associated with streptococcal TSS (1,2). Typically, pain is abrupt in onset and is severe (125,134). It commonly is present prior to tenderness or signs of localized infection (1).

The most common presenting sign is fever up to 106°F, but patients with advanced disease may present with hypothermia (125,134). As the result of decreased perfusion and/or hypoxia, CSN signs such as confusion, which is seen in approximately 50% of cases, combativeness, or coma are present (125,134). With a cutaneous portal of entry, evidence of soft tissue infection (e.g., pain, localized swelling, erythema, and tenderness) may be evident upon presentation (1). Necrotizing fasciitis or myonecrosis should be suspected when violaceous bullae are present (1). Depending on the other sites of infection, patients may present with signs and symptoms of postpartum endomyometritis, peritonitis, pelvic inflammatory disease, pharyngitis, pneumonia, or overwhelming sepsis (118,125,134).

The majority of streptococcal TSS cases characteristically present with hypotension and tachycardia out of proportion to the fever (1). Among patients initially presenting as normotensive, hypotension develops rapidly (within 4 hours) (125,134). Diffuse capillary leakage results in generalized interstitial edema in nearly all patients with streptococcal TSS (1). Although a diffuse erythroderma rash may be present and desquamate during the recovery phase, a rash is much less common than with staphylococcal TSS (1,2).

Laboratory findings with streptococcal TSS include a normal or slightly elevated white blood cell count, with a striking shift to the left (bandemia >50% may occur), decreased renal function (mean serum creatinine >2.5 normal), hypoalbuminemia, and hypocalcemia (125,134). With necrotizing fasciitis, an elevated or rising creatine phosphokinase level is present (125,134).

Adult respiratory distress syndrome has been reported in up to 55% of patients, usually manifesting after onset of hypotension (125,134). Bacteremia occurs in 60% of patients with streptococcal TSS (1).

The major complications associated with group A streptococcal soft issue infection and their frequency are given in Table 11.11. Mortality in association with streptococcal TSS is high, ranging from 30% to 70% (124,125,134,135). Among the survivors, morbidity is similarly very high (1). An estimated 50% of patients with streptococcal TSS undergo major surgical procedures, often as a life-saving procedure to address infection sites, including surgical debridement, exploratory laparotomy, hysterectomy (with or without bilateral salpingo-oophorectomy),

fasciotomy, and amputation (125,134).

Complications	Percentage of Patients
Shock	95
Adult respiratory distress syndrome	55
Renal impairment	80
Irreversible	10
Reversible	70
Bacteremia	60
Mortality	30

From Stevens DL, Tanner MH, Winship J, et al. Reappearance of scarlet fever toxin A among streptococci in the Rocky Mountain West: severe group A streptococcal infection associated with a toxic-shock-like syndrome. *N Engl J Med* 1989;321:1, with permission.

TABLE 11.11. COMPLICATIONS OF GROUP A STREPTOCOCCAL SOFT TISSUE INFECTION

A comparison of the clinical features seen in staphylococcal and streptococcal TSS is given in Table 11.12.

Feature	Staphylococcal	Streptococcal
Age	Primarily 15–36 yr	Primarily 20–50 yr
Gender	Greatest in women	Either
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality	<3%	30%–70%

NSAID, nonsteroidal antiinflammatory drug.
From Stevens DL. The toxic shock syndrome. *Infect Dis Clin North Am* 1996;10:727–746, with permission.

TABLE 11.12. COMPARISON OF STAPHYLOCOCCAL AND STREPTOCOCCAL TOXIC SHOCK SYNDROME

Stevens (1) has suggested that exposure to a virulent strain of group A streptococci usually is not sufficient by itself to cause streptococcal TSS. Rather, he noted that other factors may be required for streptococcal TSS to occur (1). Examples of such factors include (i) varicella infection, which can disrupt anatomic barriers in the skin and mucosal surfaces; (ii) influenza infection affects respiratory epithelium providing a portal of entry; (iii) viral infections may predispose the immune system to streptococcal TSS; (iv) disruption of skin barriers due to lacerations, burns, surgical incisions, intravenous drug use, and bites; (v) compromise of the integrity of the

uterine mucosal surface during the birthing process, which allows entry of group A streptococci from vaginal colonization or from hospital environment or personnel; (vi) use of nonsteroidal antiinflammatory agents (NSAIDs), which inhibit neutrophil function (chemotaxis, phagocytosis, and bacterial killing), augment cytokine production, and attenuate the cardinal manifestations of inflammation (136); and (vii) genetic predisposition to severe streptococcal infection secondary to factors such as human leukocyte antigen class II antigen type (1).

Clostridium Sordellii Toxic Shock Syndrome

Toxic shock syndrome has been associated with *C. sordellii* necrotizing subcutaneous infections in previously healthy postpartum patients (40,41,42,43 and 44). Histotoxic clostridia, such as *C. sordellii*, can produce a broad spectrum of soft tissue infections ranging from cellulitis to necrotizing fasciitis or frank myonecrosis (44). Patients initially present with gastrointestinal distress and generalized weakness. The cardinal findings associated with *C. sordellii* TSS are systemic toxicity and profound, rapidly progressive, widespread edema, often progressing to anasarca (44). The edema initially is localized to the perineum or surgical site (40,41,42,43 and 44). With *C. sordellii* TSS, cardiovascular status deteriorates rapidly, and progressive, refractory shock occurs (44).

With *C. sordellii* TSS, fever is absent or the patient presents with hypothermia. Minimal purulent discharge is present at the localized site of infection (44).

Typical laboratory findings include marked leukocytosis and left shift, hemoconcentration, evidence of DIC, and isolation of *C. sordellii* as the principal anaerobic organism from infected tissue site (44). Blood cultures are negative for pathogens, including *C. sordellii*.

DIAGNOSIS

As described earlier, TSS presents with a broad spectrum of clinical manifestations, and multiple organ systems are involved. No definitive diagnostic or confirmatory laboratory test has been developed for TSS, and none of the variety of clinical and laboratory findings are pathognomonic for the disease. Moreover, after suspecting TSS, it is necessary to differentiate among the three types of TSS: staphylococcal, streptococcal, and *C. sordellii*. It is necessary not only to differentiate TSS from a multitude of other diseases listed in Table 11.13, but also to identify the causative organism.

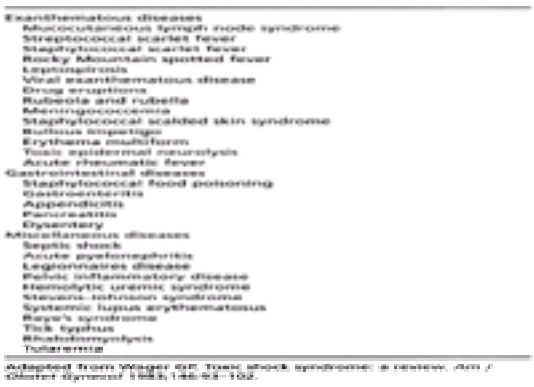


TABLE 11.13. DIFFERENTIAL DIAGNOSIS OF TOXIC SHOCK SYNDROME

Staphylococcal Toxic Shock Syndrome

An empiric diagnosis must be based on the typical constellation of clinical and laboratory findings previously described (Table 11.3, Table 11.4 and Table 11.5). Clinicians should consider the possibility of staphylococcal TSS in any patient with an unexplained febrile, exanthematous, multisystem illness, especially if the illness is associated with menstruation or a documented or suspected *S. aureus* infection. A high index of suspicion and early diagnosis are crucial to instituting appropriate therapy and gaining a favorable prognosis.

The majority of diseases on the differential diagnosis list are easily differentiated from TSS based on clinical grounds and laboratory evaluation. However, several of the conditions are very similar and may be difficult to differentiate. Streptococcal scarlet fever is unusual after 10 years of age and generally occurs secondary to an upper respiratory tract illness from which the group A b-hemolytic streptococcus can be recovered. If seen early in the disease, the rash of scarlet fever is described as a “sandpaper rash.” Late in the disease, the desquamation of scarlet fever and TSS are clinically similar, although microscopically they occur in different levels of the skin. Serum antibodies to streptococcal extracellular products, such as antistreptolysin O, are always present with scarlet fever. Since 1987, the streptococcal toxic shock-like syndrome has been recognized (23,24,25,26,27,28,29,30,31 and 32). This syndrome is caused by group A b-hemolytic streptococcus (*S. pyogenes*) and is characterized by marked systemic toxicity, rapidly progressive multisystem organ failure, and a high mortality rate (30%–60%) (30). A comparison of the common clinical findings in staphylococcal and streptococcal TSS is given in Table 11.12. Other than the association of tampon use and menstruation with staphylococcal TSS, the clinical findings most helpful in differentiating these entities are as follows: (i) rash is more common with staphylococcal TSS; (ii) tissue necrosis is more common with streptococcal TSS; and (iii) pain is common with streptococcal TSS but rare with staphylococcal TSS. Definitive differentiation relies on isolation of *S. aureus* versus *S. pyogenes.*

Mucocutaneous lymph node syndrome (Kawasaki disease) presents with a clinical picture very similar to that of staphylococcal TSS. Some investigators have suggested that this disease may be a variant form of TSS (6,7,9). However,

mucocutaneous lymph node syndrome is primarily a pediatric disease, and the majority of cases have occurred in children less than 5 years old. In addition, as noted by McKenna et al. (6), myalgias, elevated creatine phosphokinase, abdominal pain, hypotension and shock, ARDS, thrombocytopenia, and renal failure are very rare or absent in mucocutaneous lymph node disease.

Diseases such as leptospirosis, rubeola, and Rocky Mountain spotted fever are clinically strikingly similar to TSS. However, serologic testing of acute and convalescent serum can establish or rule out these diseases. In addition, *Leptospira* can be cultured from spinal fluid and/or blood.

Streptococcal Toxic Shock Syndrome

The Working Group on Severe Streptococcal Infections defined group A streptococcal TSS (32), and their proposed case definition for streptococcal TSS is given in Table 11.10. The first criterion is isolation of group A streptococci. An illness in a patient with a group A streptococcus isolated from a normally sterile site (IA) that meets the remainder of the definition can be designated as a definite case of streptococcal TSS (32). An illness in a patient with group A streptococci isolated from a nonsterile site only (IB) but that fulfills other criteria and has no other identified etiology can be designated as a probable case. The second requirement of the case definition is the presence of signs associated with severe infection, especially shock (IIA) and organ system involvement (IIB). Classification of group A streptococcal infections is given in Table 11.14. The features of streptococcal TSS can be readily recognized clinically or by routine laboratory tests (32).

I. Streptococcal toxic shock syndrome: defined by criteria in Table 11.10
II. Other invasive infections: defined by isolation of group A streptococci from a normally sterile site in patients not meeting criteria for streptococcal toxic shock syndrome
  A. Bacteremia with no identified focus
  B. Focal infections with or without bacteremia. Includes meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, septic arthritis, necrotizing fasciitis, surgical wound infections, erysipelas, and cellulitis.
III. Scarlet fever: defined by a scarlatina rash with evidence of group A streptococcal infection, most commonly pharyngotonsillitis
IV. Noninvasive infections: defined by the isolation of group A streptococci from a nonsterile site
  A. Mucous membrane: includes pharyngitis, tonsillitis, otitis media, sinusitis, vaginitis
  B. Cutaneous: includes impetigo
V. Nonsuppurative sequelae: defined by specific clinical findings with evidence of a recent group A streptococcal infection
  A. Acute rheumatic fever
  B. Acute glomerulonephritis

[a]Examples of conditions in each category are not inclusive.

TABLE 11.14. CLASSIFICATION OF GROUP A STREPTOCOCCAL INFECTION[a]

Clostridium Sordellii Toxic Shock Syndrome

Clostridium sordellii TSS should be suspected when a previously healthy woman with recent “clean” obstetric wounds or incisions presents with rapidly spreading edema that initially was localized to the perineum or surgical site and rapid cardiovascular decompensation with progressive, refractory hypotension (44). Unlike streptococcal TSS, tissue necrosis associated with *C. sordellii* TSS remains localized

to the area surrounding the wound (44).

Intraoperative frozen-section biopsies are useful for diagnosing myonecrosis associated with *C. sordellii* (44). The absence of muscle involvement on the biopsy of necrotizing subcutaneous infection strongly suggests a diagnosis of necrotizing fasciitis (44).

Definitive diagnosis requires isolation of *C. sordellii* from infected tissue. On the other hand, blood cultures are negative.

TREATMENT AND PREVENTION

Patients with suspected TSS require prompt and aggressive therapy (1,2,47,55). Initial evaluation of the patient commences simultaneously with aggressive fluid resuscitation aimed at maintaining adequate circulating volume, cardiac output, blood pressure, and perfusion of vital organs.

Staphylococcal Toxic Shock Syndrome

Initial patient evaluation requires a thorough physical examination, which includes a pelvic examination to look for and remove any tampon, diaphragm, cervical cap, or contraceptive sponge that may be present. If none of these items is present, a thorough search for a localized *S. aureus* infection must be undertaken. Cultures for *S. aureus* are obtained from the vagina, rectum, conjunctiva, oropharynx, anterior nares, and any localized sites of infection. Blood, urine, and spinal fluid also are obtained for culture.

Serum is obtained for serologic studies to rule out leptospirosis, rubeola, and Rocky Mountain spotted fever. Additional laboratory studies are obtained for a complete blood count, with differential, platelet count, and coagulation screen; electrolytes; liver function tests; calcium, phosphorus, creatine phosphokinase, BUN, creatinine, and urinalysis; chest x-ray; and electrocardiogram.

Similar to the management of septic shock, aggressive fluid replacement is the initial priority and is the cornerstone of therapy in patients with TSS. Massive amounts of fluid replacement generally are required, with 8 to 12 L per day not being uncommon (47). To facilitate and monitor administration of such massive volume replacement, placement of a Swan-Ganz catheter is necessary. This central line will allow monitoring of cardiovascular status. An arterial line is established to allow for continuous blood pressure and arterial oxygenation assessment. A urinary catheter is inserted to monitor urine output. When no blood loss has occurred, volume replacement is achieved with isotonic crystalloid solution, such as normal saline or lactated Ringer's solution; colloids such as Plasmanate or salt-poor albumin; or combinations of crystalloid and colloid. In patients with blood loss secondary to DIC, packed red blood cells and coagulation factors should be included in the fluid replacement scheme.

Fluid replacement is guided by measurement of pulmonary artery wedge pressure (PAWP), which should be maintained at 10 to 12 mm Hg (55). Shubin et al. (137) have proposed a “7-3” rule for fluid replacement in shock patients (137). A fluid bolus of 5 to 20 mL/min for 10 minutes is given. If PAWP increases more than 7 mm Hg

above baseline, the infusion is temporarily discontinued. If PAWP does not rise more than 3 mm Hg, a second similar fluid challenge is given and the “7-3” rule reapplied.

As fluid replacement is initiated, use of military antishock trousers (MAST unit) may be beneficial in producing immediate improvement in cardiac function. This unit mobilizes pooled blood from the lower extremities and lower abdomen/pelvis and returns it into the central circulation. McSwain (138) reported that the MAST unit results in an autotransfusion with 750 to 1,000 mL of autologous blood. The MAST unit is a temporizing measure. Once fluid replacement has reestablished normal perfusion blood pressure, the unit should be deflated gradually.

If aggressive volume replacement does not promptly restore blood pressure and perfusion to vital organs, use of vasopressor therapy is indicated. The drug of choice is dopamine, which in low doses has a weak b-mimetic effect that results in increased myocardial contractility and heart rate while simultaneously stimulating dopaminergic receptors that cause vasodilation of the renal, mesenteric, coronary, and cerebral vasculature (1,2). In addition, dopamine produces vasoconstriction in skeletal muscle. This results in diversion of blood from peripheral beds to vital organs (i.e., heart, brain, kidney).

Dopamine is administered by continuous intravenous infusion. An initial dose of 2 to 5 µg/kg/min is instituted, and the infusion is increased in small increments until an appropriate perfusion pressure is obtained.

As in patients with septic shock, use of glucocorticoids in the management of TSS is no longer recommended. Their efficacy or necessity in TSS has not been demonstrated.

Two additional therapeutic modalities have been suggested for management of TSS patients (as well as septic shock patients) with intractable hypotension. Several studies have demonstrated successful results with the use of naloxone (Narcan) (139,140). This narcotic antagonist could block the action of endorphins present in elevated levels in stressed patients, profoundly depressing the cardiovascular system. Although not of proven value in TSS, this approach deserves further investigation. Duff (55) has suggested that hemodialysis might remove the toxin responsible for the hypotension. Such an approach has been used with success in clostridial septicotoxemia secondary to the exotoxins of *C. perfringens*. This approach has not been evaluated adequately in TSS.

Although b-lactamase–resistant, antistaphylococcal antibiotics have not been demonstrated to shorten the acute episode of TSS or to be necessary for clinical response in the acute episode, they are recommended as part of the therapeutic approach. First, they are advisable because of the risk of bacteremia with *S. aureus.* More importantly, patients who received b-lactamase–resistant, antistaphylococcal antibiotics had a significantly lower rate of TSS recurrences (7,9,11). Available choices include methicillin, nafcillin, and oxacillin. For penicillin-allergic patients, vancomycin, clindamycin, and gentamicin are alternatives.

A major objective in the management of TSS is preventing ARDS, which is one of the leading causes of death in TSS and is associated with very high mortality rates when it complicates septic shock. Oxygen is administered by mask or nasal cannula at the initiation of therapy. Arterial blood gases are monitored frequently to detect

hypoxia and/or metabolic acidosis. Close monitoring of fluid replacement is mandatory to avoid excessive fluid replacement. There should be no hesitancy to intubate the patient and institute mechanical ventilation with the earliest signs of decreased pulmonary compliance. With such an aggressive approach, irreversible hypoxic damage to the pulmonary vasculature hopefully will be prevented.

Additional therapeutic measures may be necessary on an individual basis, depending on the clinical presentation of TSS. Coagulation abnormalities are treated with fresh frozen plasma, cryoprecipitate, fresh whole blood, and/or platelets. Calcium supplementation may be necessary if hypocalcemia and/or cardiac dysfunction is present. Electrolyte abnormalities must be corrected by administration of electrolyte solutions. Dialysis may be necessary in cases of acute renal failure. Finally, in nonmenstrual cases of TSS, a thorough search for localized *S. aureus* infection(s) must be undertaken. Such infection sites must be managed appropriately, as indicated by the particular type of infection (i.e., incision and drainage of abscesses, debridement of necrotic tissue). Chesney et al. (11) have suggested that consideration be given to administering intravenous immunoglobulin (IVIG) to patients severely ill with TSS. High levels of antibody to TSST-1 have been demonstrated in IVIG (141).

Recommendations have been made to reduce the risk of TSS (6). Women can significantly decrease their risk of developing TSS by not using tampons. The risk also may be reduced by avoiding continuous tampon use and alternating tampon use with napkins. Based on studies demonstrating a very significant increased risk to develop TSS among users of high-absorbency tampons (40,60), only low-absorbency tampons are available in the United States. Women, especially young adolescents, must be educated about the signs and symptoms of TSS. They should be warned that if such signs and symptoms occur, the tampon must be removed and medical care sought promptly. Women with a previous history of TSS should, ideally, not use tampons.

In summary, good results in the management of TSS depend on a high index of suspicion; prompt and aggressive fluid replacement; close monitoring of cardiovascular status, respiratory status, and urine output; and prevention or early recognition, and treatment, of ARDS.

Streptococcal Toxic Shock Syndrome

Unlike in staphylococcal TSS where antibiotic therapy has not been shown to affect the acute clinical response, antibiotic therapy is a critical component of treating streptococcal TSS. Group A streptococci are very sensitive to b-lactam antibiotics, and multiple studies have demonstrated the efficacy of penicillin in treating cutaneous infections and pharyngitis due to penicillin (1). However, most aggressive, invasive group A streptococcal infections (e.g., necrotizing fasciitis, subcutaneous gangrene, myositis) have been shown to respond less well to penicillin (1,2). The explanation for this clinical finding relates to growth rates of the organism and the quantity of penicillin-binding sites present on the group A streptococci (1,2). With mild infections or early in the infection, organisms are present in low concentrations and are rapidly growing (1,2). Subsequently, in the later stages of infection, growth slows and there is a loss of penicillin-binding proteins. This loss of binding sites decreases the effectiveness of b-lactam antibiotics.

As a result, clindamycin in a dose of 900 mg intravenously every 8 hours has become the drug of choice for treating streptococcal TSS (1,2). Several factors have been linked to the greater efficacy of clindamycin (1,2): (i) inoculum size or stage of growth does not affect efficacy; (ii) clindamycin is a potent suppressor of bacterial toxin synthesis; (iii) clindamycin facilitates phagocytosis of *S. pyogenes* by inhibiting M protein synthesis; (iv) clindamycin suppresses synthesis of penicillin-binding proteins, which are enzymes involved in cell wall synthesis; (v) clindamycin has a longer postantibiotic effect than most b-lactam antibiotics; and (vi) clindamycin suppresses lipopolysaccharide-induced monocyte synthesis of TNF-a by 40% (1,2,142,143). Erythromycin (1 g intravenously every 6 hours) is less active than clindamycin but better than penicillin (142). Although single-agent antimicrobial therapy is effective against group A streptococci, combination broad-spectrum antimicrobial therapy generally is recommended due to the severe nature of these group A streptococcal infection (2).

Although antibiotic treatment is extremely, important additional intervention including prompt and aggressive exploration and debridement of suspected deep-seated group A streptococcal infection are required (1). Early surgical intervention is often a lifesaving step. General supportive measures as described in the management of staphylococcal TSS are an important component of managing patients with suspected streptococcal TSS (1,2).

Intravenous immunoglobulin has been used to neutralize toxin as well as cytokines (144). Pooled IVIG contains antibodies to streptococcal superantigens and decreases production of inflammatory cytokines (1,2). Weiss and Laverdiere (142) reported that, in patients with streptococcal TSS, IVIG significantly decreased the death rate (40% vs. 80%). Additional reports have shown dramatic improvement with IVIG (1,144). The recommended dose for IVIG is 2g/kg for 2 days.

Clostridium Sordellii Toxic Shock Syndrome

Management of *C. sordellii* TSS among pregnant women is similar to the treatment of *C. perfringens* myonecrosis and/or septicotoxemia. Treatment includes aggressive and early surgical debridement, broad-spectrum antimicrobial agents, high-dose penicillin, hyperbaric oxygen therapy, and intensive supportive care.

Despite such aggressive therapy, all reported maternal infections, to date, have been fatal. Cardiovascular collapse secondary to marked “third spacing” with sequestration of fluid has been the presumed cause of death (44). Once *C. sordellii* commences production of the exotoxins (especially lethal toxin), aggressive debridement and antibiotic therapy do not appear capable of reversing the pathologic chain of events initiated by the exotoxin (44).

It appears that either neutralization or elimination of the exotoxins is required if survival is to occur (44). However, exogenous antisera are not available. Use of plasma exchange to diminish toxin levels might be of benefit. Use of this approach in the presence of the significant hypotension associated with *C. sordellii* TSS is problematic (44).

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12

INFECTIOUS VULVOVAGINITIS

Symptoms of vulvovaginitis, which include discharge, odor, itching, and vaginal discomfort, account for a considerable proportion of outpatient gynecologic visits. Although diagnosis and therapy of vulvovaginitis is straightforward in most cases, many patients experience persistence or recurrence, and still others who have less distinctive types of vaginitis do not receive satisfactory therapy. Developments in the last 5 years have included improved knowledge of the complications associated with vaginitis (upper genital tract infection and adverse pregnancy complications), new diagnostic techniques, and refinements of therapy.

PREVALENCE AND DISTRIBUTION OF VAGINITIS

In their classic paper, Gardner and Dukes (1) analyzed 1,181 private patients with symptoms of vaginitis or with gross evidence of vaginitis on inspection. They described normal vaginal secretions as usually white and curdy (i.e., not homogeneous), with a pH of 4.0 to 4.7. Their findings are summarized in Table 12.1. The most common type of vaginitis was what they called “nonspecific vaginitis” (now called bacterial vaginosis [BV]). Trichomoniasis and candidiasis each accounted for about one fourth of cases.

Clinical Diagnosis	No. of Cases	Percentage of All Patients	Percentage of Cases of Vaginitis
Trichomoniasis[a]	71	6.0	24
Moniliasis[b]	79	6.7	27
Nonspecific vaginitis[c]	127	10.8	41
Gonorrhea	1	0.1	
Chancroid	1	0.1	
Granuloma inguinale	1	0.1	
Other bacterial vaginitis	11	1.0	4

[a]Trichomoniasis based on typical symptoms and positive smear.
[b]Moniliasis based on typical signs, symptoms, and positive smear.
[c]Nonspecific vaginitis, which was called Haemophilus vaginalis vaginitis by these authors, was based on typical findings and a positive culture of H. vaginalis.
Adapted from Gardner H, Dukes CD. Haemophilus vaginalis vaginitis: a newly defined specific infection previously classified "nonspecific" vaginitis. Am J Obstet Gynecol 1955;69:962.

TABLE 12.1. ETIOLOGY OF INFECTIOUS VAGINITIDES IN 1,181 PATIENTS

Vaginal symptoms occur commonly. Trichomoniasis, moniliasis, and BV account for the vast majority of cases, but some cases (1%–10%) cannot be accounted for by these three diagnoses. Further, the prevalence of vulvovaginal organisms varies from population to population. Asymptomatic women commonly will harbor yeasts, *Trichomonas vaginalis* or *Gardnerella vaginalis.*

GENERAL DIAGNOSTIC APPROACH TO INFECTIOUS VULVOVAGINITIS

Most cases of infectious vulvovaginitis can be diagnosed with a few inexpensive tests, provided the tests are used and interpreted properly.

In all cases, the physical examination should note the following: vulvar erythema; edema; excoriation or lesions; and color, amount, and consistency of the vaginal discharge. Normal vaginal secretions are heterogenous. The cervix should be examined for eversion, friability, and color of mucus.

For patients with vaginal discharge or irritation, the following tests are indicated:

- pH (using a paper that will distinguish pH values in the range from 4.0 to 5.0 (Fig. 12.1)

FIGURE 12.1. pH paper used in the differential diagnosis of vulvovaginitis. The pH range is from 4.0 to 7.0.

- Amine (“fishy”) odor by adding a drop of discharge to a drop of 10% potassium hydroxide (KOH) solution
- Saline preparation for true clue cells and trichomonads
- KOH preparation for hyphae and pseudomycelia of yeasts
- Culture for yeasts, if the other tests are nondiagnostic
- Saline preparation of an endocervical smear (to detect microscopic cervicitis)

True “clue cells” (Fig. 12.2) are so heavily stippled with adherent bacteria as to obscure the cell margin. Normal epithelial cells commonly have some adherent

bacteria (Fig. 12.3).

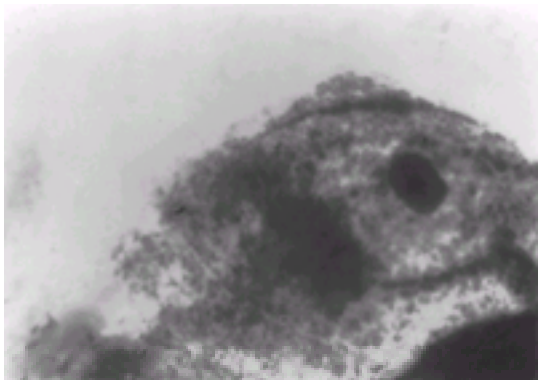

FIGURE 12.2. Vaginal Gram stain showing a true clue cell and abnormal bacteria characteristic of bacterial vaginosis.

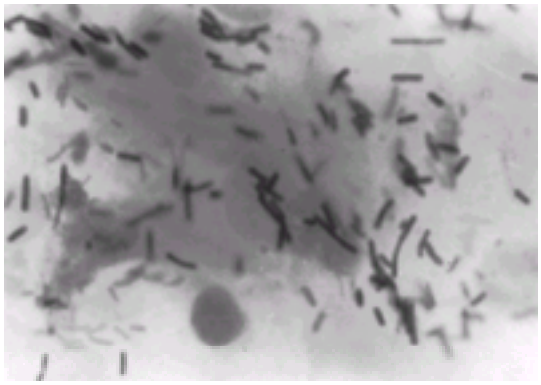

FIGURE 12.3. Gram stain showing normal vaginal flora with a predominance of *Lactobacillus* morphotypes.

Culturing for *G. vaginalis* is not indicated. Although 95% of women with BV are positive (when selective media are used), so are 40% of women with normal secretions.

The Gram stain may be of help in diagnosing vaginitis, as the variety and numbers of bacteria can be readily identified, but this technique is infrequently used clinically (see section on bacterial vaginosis).

Diagnostic criteria are given in Table 12.2. Approximately 8% to 10% of patients with abnormal vulvovaginal symptoms will not be diagnosed by the tests described. In these patients, cervicitis due to gonorrhea or chlamydia should be excluded. Cervicitis due to gonorrhea or chlamydia should be excluded by specific testing. In

addition, a saline preparation of an endocervical smear should be examined microscopically to detect evidence of cervicitis, which often is nongonococcal and nonchlamydial in origin. Although the etiology of this cervicitis is not clearly elucidated, empiric treatment with a quinolone, erythromycin, doxycycline, or azithromycin is reasonable in patients with persistent symptoms. Because of the limited sensitivity of the wet mount for trichomonads (estimated at 50%–80%), additional diagnostic tests have been developed. Media for culturing trichomoniasis are available commercially, as Diamond or Trichosel media or as the InPouch TV system (see section on trichomoniasis). Some women presenting with symptoms of vulvar burning and irritation may be characterized as having vulvodynia or, alternatively, vulvar vestibulitis. This condition most likely is neuropathic rather than infectious in origin. This entity has a fairly characteristic presentation, marked by chronic vulvar (rather than vaginal) symptoms, point tenderness along the vaginal vestibule, and perhaps erythema in the vestibular glands at the five and seven o'clock positions (i.e., posteriorly at the introitus, just to the right and left of the midline).

Feature	Normal	Bacterial Vaginosis	Trichomonas	Yeast
Appearance	White, flocular, high viscosity	Gray, white, milky/creamy	Gray, yellow, greenish, or white, homogeneous, often frothy	White, often curdy
pH	≤4.5	>4.5	>4.5	≤4.5
Amine odor	Absent	Present	Absent	Absent
Clue cells	Absent	Present	Absent	Absent
Trichomonads	Absent	Absent	Present	Absent
Mycelia	Absent	Absent	Absent	Present

TABLE 12.2. CHARACTERISTICS OF NORMAL SECRETIONS AND VAGINITIS

TRICHOMONIASIS

Trichomoniasis is caused by *T. vaginalis,* a protozoan first described in 1836. The organism has been responsible for approximately one fourth of all cases of clinically evident vaginal infections (1), but its prevalence appears to be decreasing lately (2). Previous estimates placed the prevalence at 3% to 5%, with a range of 2% to 3% in middle-class women to 56% in women attending sexually transmitted disease (STD) clinics (3). Approximately 50% of women with *T. vaginalis* are asymptomatic, but about 30% of these asymptomatic women develop symptoms when they are observed for 6 months (3).

Among symptomatic women with trichomoniasis, the vaginal secretions usually are copious, homogeneous, and malodorous, with a pH above 4.5. A frothy, yellow-green discharge often is cited as the typical finding, but, in objective series, frothiness was detected in only 12% to 34% (1). Gardner and Dukes (1) described the color of the discharge as gray in 46% of cases, yellow-green in 36%, and yellow-green in 10%. Punctate mucosal hemorrhages of the cervix, the so-called

strawberry or “flea-bitten” cervix, are seen infrequently with the naked eye but are seen frequently with colposcopy. Because of the variations in signs and symptoms, one cannot rely on these findings.

Under most circumstances, the clinical diagnosis can be confirmed by microscopic examination of a wet mount, made by mixing a drop of secretions with saline on a slide. Because trichomoniasis may produce a heavy polymorphonuclear infiltrate, it is easy to miss the trichomonads. One must examine the preparation in an area with relatively few white cells. Usually, the trichomonads are evident because of the extreme activity of these flagellates in freshly made preparations. A helpful clue for microscopic diagnosis of trichomoniasis is using fresh saline (intended for intravenous use) with no preservative. Most reports have found the sensitivity of culture to be greater than that of wet mounts (4). The sensitivity of clinical microscopy varies with the experience and thoroughness of the examiner (3). Overall, sensitivity varied from as low as 42% to as high as 92%. When experienced technicians perform the test, the sensitivity runs at about 80%, compared with culture; when busy clinicians perform it, the sensitivity drops to about 50%.

Culturing currently is considered the best method for making the diagnosis. Culture for *T. vaginalis* is not difficult, but special media, such as Diamond or Kupferberg medium, is needed. A drop or swabful of the vaginal secretions is placed in the broth, which is incubated. A drop of the media is examined daily under the microscope for 5 to 7 days for appearance of the motile trichomonads. Because there is limited demand for *T. vaginalis* cultures, few clinical laboratories have this available, even though the media are commercially available. In a comparison of a commercially available kit system (InPouch TV) to Diamond modified medium for culture of *T. vaginalis* from vaginal secretions, both culture techniques performed with similar high sensitivity (5).

The diagnosis of trichomoniasis is possible on a Papanicolaou (Pap) smear, but the sensitivity of this method is modest (52%–67%). There is a low specificity, even when the smear is prepared with a vital stain such as acridine orange (6,7).

New diagnostic methods using monoclonal antibodies, enzyme-linked immunosorbent assay, and latex agglutination have been introduced. Although initial reports show encouraging results, there has not been much use in the clinical setting to determine the practical reliability of these (3,8). Several publications also have assessed a *T. vaginalis* polymerase chain reaction (PCR) test. Although these diagnostic tests each have used different PCR primers, each test has reported higher sensitivity with the PCR than with wet-mount microscopy, culture on Diamond or modified Kupferberg medium, or Pap smear. The PCR test also appears to be highly specific without interaction with other species of *Trichomonas* other than *T. vaginalis* and without cross-reactivity with other human parasites or other human STDs such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae.* The improved sensitivity of PCR appears to apply both to women without and women with symptoms of vaginal discharge (9). One additional advantage of the PCR test is that satisfactory specimens can be obtained by self-collection from the distal vagina, which eliminates the requirement for a vaginal speculum examination (6,7,10,11 and 12)

Urine sediment can be examined for trichomonads, and this is the preferred site for detection in males. The sediment can be cultured as well as inspected

microscopically.

The diagnosis of trichomoniasis is difficult, limited by the recognized modest sensitivity of the wet mount. For most practice situations, however, the wet mount continues to be the diagnostic technique of choice, even among experts (2). In special circumstances, culture using either Diamond medium or the InPouch Kit seems important, and PCR technology may become commercially available within the next few years.

The only treatment for trichomoniasis available in the United States is metronidazole (Flagyl). Related 5-nitroimidazole derivatives (tinidazole, ornidazole) are available in other countries. In the early 1970s, evidence indicated that metronidazole was carcinogenic in certain rodent species but not in others. When tumors evolved, it was only after chronic, high-dose use, making the application of these data to humans difficult. The United States Food and Drug Administration (FDA) interpreted the data as showing a very low risk of human carcinogenesis and denied a petition to remove metronidazole from the market (13). Later, a study from the Mayo Clinic provided data on 771 women given metronidazole for trichomoniasis (14). With surveillance of 10 to 20 years, these investigators found no appreciable carcinogenicity attributable to metronidazole. Additional recent information has provided further reassurance. In a study of 1,387 women who filled prescriptions for metronidazole in pregnancy, there was no excess of overall birth defects (in their offspring), compared with 1,387 control women (risk ratio [RR], 1.2, 95% confidence interval [CI], 0.9—–1.6). The authors also were unable to find an excess risk in any category of birth defects (15).

In 1976, in view of concerns about carcinogenicity, there was a reduction in standard dose of metronidazole (250 mg orally three times a day in women) from 10 to 7 days, and topical metronidazole preparations for treatment of trichomoniasis were removed from the market (13). A single 2-g dose was evaluated and found to be effective (7). Direct comparisons of the 7-day and single-dose regimens have found them to be equivalent (16). Cure rates with either regimen have varied from 86% to 97%, and side effects (mainly nausea) have not been significantly different between the two regimens. The CDC guidelines recommend single-dose treatment as the regimen of choice (17).

Possible causes of failure of metronidazole therapy include (a) pharmacokinetic problems in either absorption or delivery to the infected site, (b) inactivation of metronidazole by vaginal bacteria, (c) interference by other drugs, (d) resistance to metronidazole, (e) noncompliance or gastrointestinal intolerance, and (f) reinfection. In the past, resistance was discounted, but development of a suitable aerobic *in vitro* assay has permitted the demonstration of resistance in strains from Europe and the United States (18).

Sexual partners should be treated. Although there are concerns raised by prescribing metronidazole to the male partner who does not come to the office or clinic, the CDC clearly recommends concurrent treatment of male partners of women with trichomoniasis (Table 12.3)(17).

TABLE 12.3. CENTERS FOR DISEASE CONTROL AND PREVENTION RECOMMENDED REGIMENS FOR *TRICHOMONAS VAGINALIS* VAGINITIS

Use of metronidazole occasionally is accompanied by headache, metallic or bitter aftertaste, or nausea and vomiting. Seizures and central nervous system toxicity can accompany metronidazole therapy, almost exclusively in patients on exceedingly high doses (>3 g/day). Blood dyscrasias are rare consequences, but, in the product information, total and differential leukocyte counts are recommended before and after treatment, especially when a second course is necessary. Alcohol should be avoided during treatment and for 3 days afterward.

Metronidazole gel (0.75%) has become available and is indicated for treating BV. It has not been evaluated for trichomoniasis and should not be used for this infection in view of the poor efficacy of past local therapies. The FDA has approved a new preparation of metronidazole, marketed as Flagyl 375™ mg, twice daily for 7 days for treatment of trichomoniasis. This approval was based on the pharmacokinetic equivalency of this regimen with metronidazole 250 mg three times daily for 7 days. No clinical data are available to demonstrate clinical equivalency of the two regimens (17).

Follow-up examination is not recommended for patients who become asymptomatic after treatment.

For treatment of trichomoniasis in pregnancy, metronidazole is recommended by the CDC in a single 2-g dose (17).

Symptomatic nonpregnant women with documented trichomoniasis should be treated to prevent sexual transmission and future symptomatic infection. Symptomatic pregnant women with trichomoniasis should be treated with 2 g of metronidazole in a single dose. The CDC guidelines no longer restrict use of metronidazole to the second or third trimester. For pregnant women with asymptomatic trichomoniasis, the decision to treat is a dilemma. There is some evidence linking this infection to adverse pregnancy outcomes (see later), and sexual transmission remains a possibility. In selected circumstances, such as in patients undergoing cerclage or patients presenting in preterm labor, screening for and treatment of *T. vaginalis* may still be a very reasonable approach. However, a recent

treatment trial conducted by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Unit Network concluded that metronidazole treatment increased the risk of preterm birth in asymptomatic women with trichomoniasis. In a multicenter, double-blind, placebo-controlled trial, women who were culture positive for trichomoniasis were randomized at 16 to 23 weeks of gestation to receive either metronidazole or placebo. The metronidazole regimen was 2 g given under observation and another dose 48 hours later. Sexual partners of women in both groups were given prescriptions for metronidazole. The regimen was repeated at 24 to 29 weeks of gestation. The two groups, with approximately 300 women in each group, did not differ significantly in terms of demographic characteristics. However, total preterm birth was significantly greater in the group receiving metronidazole (19% vs. 10.7%; RR, 1.8; 95% CI, 1.19—–2.66). There were significant increases in preterm births due to preterm labor (10% vs. 3.5%; RR, 2.87; 95 CI, 1.43–5.75). There were no significant differences in preterm births due to preterm premature rupture of the membranes (PROM), births at less than 32 weeks, birthweights less than 2,500 g, or birthweights less than 1,500 g. The risk of preterm birth in the metronidazole group was elevated among women with a prior preterm birth (RR, 1.93; 95 CI, 0.93–3.98; $p > 0.05$) (18). In view of the surprising results of this trial, treatment of asymptomatic women in pregnancy with trichomoniasis cannot be recommended.

Treatment for patients with human immunodeficiency virus (HIV) infection and trichomoniasis currently is the same as the treatment for patients without HIV (18).

When a patient has apparent persistence of *T. vaginalis* despite appropriate initial therapy, determine whether there has been compliance by both the patient and her sexual partner(s). Exclude interference by other medications such as phenytoin or phenobarbital, which induce microsomal liver enzymes and accelerate elimination of metronidazole.

If these problems are excluded, presumptive treatment for a relatively resistant strain is appropriate. Relatively resistant strains have become increasingly common. Muller and colleagues (19) determined *in vitro* susceptibility to metronidazole in 146 isolates from patients who responded to a single 2-g oral dose. The mean aerobic minimum lethal concentration (MLC) was 24.1 µg/mL. In comparison, the mean aerobic MLC was 195.5 µg/mL in 53 isolates from patients who had persistent infection. The corresponding mean anaerobic MLC values were 1.6 and 5.0 µg/mL (19).

Lossick and colleagues (20,21) reported treatment in 53 women with persistent infection. Eighty percent of the women (27/31 from whom clinical follow-up data were available) were ultimately cured with a higher dose of metronidazole. Regimens ranged from 2 to 4 g/day for 5 to 14 days, often with vaginal insertion of a 500-mg oral tablet nightly. Doses greater than 3 g/day were accompanied by a high risk of serious side effects, including irreversible neurologic problems. Further intravenous administration appeared to have no advantage.

The CDC recommendations for treatment failures are re-treatment with metronidazole 500 mg twice daily for 7 days and, if repeated failure occurs, a single 2-g dose once daily for 3 to 5 days. For patients who still have persistent infection, the CDC recommendation is to exclude reinfection, evaluate *in vitro* susceptibility of the isolate, and manage “in consultation with an expert” (17). Consultation is available through the CDC. We check a complete blood count before repeat

high-dose treatment.

Cost-effective alternatives to metronidazole are not available. Patients who have severe vaginal trichomoniasis and serious adverse reactions to metronidazole may be managed by desensitization. In a report of two patients, women were given incremental intravenous doses of metronidazole, beginning at 5 µg and building up to 125 mg stepwise at 15- to 20-minute intervals. Oral doses then were given up to 2 g orally. It is important to note that this desensitization approach was carried out after obtaining a documented history and a positive wheal test after application of metronidazole gel to the vaginal mucosa. The desensitization was performed in a monitored bed with additional precautions that included placement of two large intravenous lines and availability of a cardiopulmonary resuscitation team. In both cases, the desensitization was carried out without complications, and both patients were cured (22).

One report described resolution of resistant vaginal trichomoniasis when the patient used intravaginal nonoxynol-9 (23).

Prevention of trichomoniasis is achieved by using safe sexual practices, which include limiting numbers of sexual partners, using condoms, and treating sexual partners.

Trichomonas vaginalis has not been linked, by itself, to genital tract cancer, infertility, abortion, or endometritis. However, as an STD, it should prompt detection of other STDs. Trichomoniasis has been linked to BV, which has been associated with several obstetric and gynecologic complications (see later). Trichomoniasis has been associated with adverse pregnancy outcomes, such as PROM and premature birth (24). One treatment trial performed to determine whether treatment of trichomoniasis in pregnancy reduces such adverse outcomes showed an increase in adverse outcomes in the treated group (18). This subject is discussed in detail in Chapter 19.

YEAST INFECTION

Yeasts are commonly isolated in the female lower genital tract, with rates of 22% among asymptomatic college women, 26% among patients in an STD clinic, and 39% among women with vulvovaginal symptoms (25). It is estimated that 75% of women will have at least one episode of yeast vulvovaginitis, with 4% to 45% having two or more episodes (17). In all studies, *Candida albicans* was the predominant yeast isolate (in approximately 90% of cases), with *Candida glabrata* and other *Candida* sp making up the remainder. Among patients with a positive culture for *C. albicans,* Oriel and coworkers (25) reported vaginal pruritus with or without discharge in 50% and discharge alone in 30%.

Commonly noted predisposing features to growth of yeast in the vagina are glycosuria, diabetes mellitus, pregnancy, obesity, and recent use of antibiotics, steroids, or immunosuppressants. Pregnancy is associated with an increased vaginal carriage rate, increased susceptibility to infection, and lower cure rates. The exact mechanism is uncertain, but pregnancy may act to increase glycogen in the vaginal epithelium, or pregnancy may provide a positive hormonal effect for yeasts. Antibiotics that most commonly result in yeast colonization are ampicillin, tetracycline, and cephalosporins. After 2 weeks of tetracycline use, vaginal carriage

increased from 10% to 30%. Presumably, antibiotics suppress normal bacterial population and allow opportunistic colonization by yeasts. Prophylactic local antifungal agents are an appropriate measure in patients susceptible to yeast infections when they require antibiotics for other infections.

In a population of women attending an urban STD clinic, risk factors for a positive genital *C. albicans* culture included condom use, presentation in the second half of the cycle, sexual intercourse more than four times per month, recent antibiotic use, young age, past gonococcal, infection and absence of current gonorrhea or BV (26).

The role of oral contraceptives (OCs) is controversial (25). Oriel et al. (25) found that OC users were more likely to have yeast isolates in vaginal cultures (32% of 241 women taking OCs vs. 18% of women not taking OCs), but symptoms or signs of vaginal yeast infection were not increased (23% OC vs. 26% no OC). Other investigators also reported increased vaginal carriage among OC users. However, recent studies of low-dose OCs have consistently reported no increase in *Candida* isolation among OC users. Proposed mechanisms include increased adherence or receptivity, increased vaginal glycogen, and increased yeast virulence. It is commonly suggested that wearing tight-fitting undergarments predisposes to yeast infection by increasing local humidity and temperature.

Yeasts usually are not acquired through sexual intercourse (17). Evidence supporting sexual transmission in yeast vulvovaginitis includes (a) a fourfold increase in yeast colonization in male partners of infected women and (b) isolation of the same strains in infected couples. Further, in a recent case-control study of 85 students with vulvovaginal candidiasis, Foxman (27) reported that frequent intercourse (defined as seven or more times per week) was the strongest risk factor. The odds ratio was 4.3 (95% CI, 1.4–12.9) compared with student health service controls with no intercourse (27). However, epidemiologic evidence against sexual transmission includes (a) no direct association between yeast infection and other STDs, (b) no difference in yeast isolation rates in STD versus non-STD populations, and (c) absence of any study showing that treatment of the male partner benefits the female. Routine treatment of sexual partners is not recommended, but may be considered for women with recurrent infection (17). These recommendations suggest treatment of male partners who have balanitis, as evidenced by erythematous areas of the glans with local pruritus or irritation. Topical treatment to relieve symptoms is recommended such cases.

Despite much anecdotal information, purported risk factors, including wiping from back to front after using the toilet, use of feminine hygiene products, type of clothing, diet, and stress, showed no association with vulvovaginal candidiasis among college women (27).

Kalo-Klein and Witkin (28) pointed out that hormonal status may influence the pathogenicity of *Candida* by modulation of immune system activity. They examined the influence of the phase of the menstrual cycle on the cellular immune response to *C. albicans,* the efficiency of *C. albicans* germination in sera, and the ability of products from activated lymphoid cells to inhibit germination. In the luteal phase, host responses to *C. albicans* were decreased.

The characteristic findings of vaginal candidiasis are reddened vulval or vaginal areas with vulval scaling, edema, or excoriation, and raised, white, or yellow

adherent vaginal plaques. However, Oriel et al. (25) noted such findings in only 38% of women with positive cultures for *C. albicans.*

The diagnosis can be confirmed by observing mycelia and/or pseudohyphae upon direct microscopy in a 10% KOH preparation, but this is a test with limited sensitivity. In the study by Oriel et al. (25), only half of the patients with positive cultures showed organisms on direct microscopy, and the women with the most florid findings often gave positive results only by culture. On the other hand, Van Slyke et al. (29) found that, among symptomatic patients, the KOH wet mount was "usually sufficient for office use." Compared with cultures, direct microscopy gave 2.3% false-positive and 6.2% false-negative results.

McCormack et al. (30) helped place the role of vaginal cultures in perspective. Among 144 women, 42 were culture positive for yeasts (30). Of these patients, 25 (60%) had vulvovaginal itching or irritation. Of the 42 culture-positive women, eight also had positive KOH preparations, and 7 (88%) of these 8 women were symptomatic. In comparison, the 34 remaining culture-positive women had negative KOH preparations, and 18 (53%) of these 34 women were symptomatic. Thus, only seven of 25 culture-positive and symptomatic women had positive KOH preparations. Interestingly, of 102 culture-negative (and KOH-negative) women, 16 (16%) had itching or irritation. McCormack et al. recommended obtaining a fungal culture for patients who have symptoms and a negative KOH preparation, before excluding yeast vulvovaginitis.

A vaginal yeast culture may reveal that the infecting species is a non–*C. albicans* variety. In the Wayne State University vaginitis clinic in Detroit, approximately 10% of all yeasts isolated are *Torulopsis* glabrata (31). In Connecticut, Horowitz et al. (32) found that *Candida tropicalis* accounted for fully 23% of all genital fungal infections, second only to *C. albicans,* which accounted for 65% of isolates. In comparison to the Detroit reports, this group found *Candida (Torulopsis) glabrata* in less than 1% of cases. Eight other species of yeast were isolated, all infrequently, by the Connecticut group. Because these reporting groups saw referral populations, it is possible that their respective rates of non–*C. albicans* species were higher than those seen in most practices. Although these reports are preliminary, they suggest that infection with non–*C. albicans* species may be more difficult to treat and more likely to recur.

The vaginal pH of women with yeast vulvovaginitis is normal (<4.5) (Table 12.2).

Rapid diagnostic techniques using technologies such as latex agglutination appear promising, but these tests have not been used in the clinical setting (33).

Treatment of acute yeast infections results in relief of symptoms and eradication of yeasts in 80% to 90% of patients, but recurrence of infection is a common problem. In general, predisposing factors should be eliminated, when possible, but this most likely will already have been done. A useful classification of candidal vaginitis for the purpose of treatment is given in Table 12.4. Candidal vaginitis is classified as uncomplicated or complicated. The former occurs in approximately 90% of patients, and treatment with a short course of either an oral or topical therapy is recommended with any regimen, including single-dose regimens. On the other hand, complicated cases occur in about 10% of patients and require an antimycotic agent for 7 or more days (34). Effective commercial preparations are listed in Table 12.5. Nystatin applied vaginally often has been less effective in the initial treatment of

routine cases and has the added disadvantage of needing a 14-day course.

Feature	Uncomplicated	Complicated
Severity	Mild or moderate	Severe
Frequency	Sporatic	Recurrent
Organism	Candida albicans	Non-albicans species of Candida
Host	Normal	Abnormal (uncontrolled diabetes mellitus)

From Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000;30:662-678, with permission.

TABLE 12.4. CLASSIFICATION OF CANDIDAL VAGINITIS

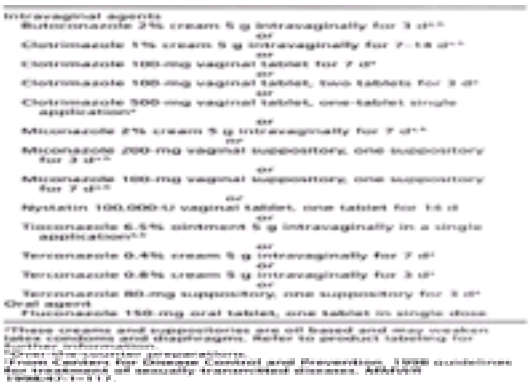

TABLE 12.5. RECOMMENDED REGIMENS FOR INITIAL TREATMENT OF CANDIDAL VULVOVAGINITIS

As shown in Table 2.5, there is a proliferation of recommended regimens for the initial treatment of candidal vulvovaginitis. Among the intravaginal agents, none has demonstrated superior efficacy, and the practitioner is able to choose from regimens offered in a course from a single dose to 3 to 7 days.

With many of these preparations available over the counter, one must be aware that self-diagnosis of yeast vaginitis is unreliable. Incorrect self-diagnosis results in overuse of topical and fungal agents, with subsequent risks of contact or irritant vulvar dermatitis and delayed diagnosis of other conditions such as STDs, vulvodynia, vulvar dystrophies, and even vulvar neoplasia (34). Self-medication with over-the-counter medications is recommended only for women who previously have been diagnosed with vulvovaginal candidiasis and who have recurrence of the same symptoms. Any women whose symptoms persist after using an over-the-counter preparation or has recurrence of symptoms within 2 months should seek medical

care according to the CDC guidelines (17).

Gentian violet (1% solution) may be used in cases of florid candidiasis to give acute symptomatic relief, but it may be messy and result in marked drying and itching if used continuously.

In 1981, Van Slyke and colleagues (29) reported excellent results with boric acid powder (600 mg in a size 0 gelatin capsule) used daily for 14 days. In a double-blind study of boric acid versus capsules containing 100,000 units of nystatin (in cornstarch), cure rates were significantly better with boric acid (92% at 7 to 10 days after treatment vs. 64% with nystatin) ($p = 0.001$). There were no serious adverse effects from either preparation, but patients using boric acid capsulates often noted a slight watery discharge. Blood boron levels indicated little absorption from the vaginal preparation. However, because boric acid in large doses is toxic, the capsules or powder must be kept out of reach of small children. Boric acid capsules also should be avoided in pregnancy. A major advantage of this treatment is its low cost. If 14 capsules and 600 mg of boric acid are prescribed, the total cost is approximately $3.00.

Many women with recurrent yeast infection will inquire about the benefits of ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for recurrent infection. One study reported that daily ingestion of 8 oz of yogurt containing *L. acidophilus* decreased both candidal colonization and infection (35). In contrast, another study showed no decrease in the incidence of candidal vulvovaginitis in women consuming yogurt containing *L. acidophilus* versus women ingesting a yogurt that was pasteurized and contained no *L. acidophilus.* Interestingly, there was an overall reduction in percentage of patients in both groups, but it was unclear whether this was due to consumption of yogurt per se or simply an observation of the natural history of recurrent yeast infections (36). Yogurt brands vary in their content of lactobacilli. Brands that have the most favorable strains include Dannon and Yoplait. It is important to advise patients to look for a label that says “contains live cultures” or a similar statement. Some pasteurized products have lactobacilli added later. The benefit of either oral ingestion or vaginal application of lactobacilli is not established, but may be used in some patients as it is unlikely to cause any adverse effects.

The availability of ketoconazole, an effective oral preparation for treatment of fungal infections, provided a new approach to therapy of vaginal yeast infections (37). It is an imidazole antifungal drug, structurally related to miconazole, and is effective in a variety of superficial and systemic mycoses. The mechanism of action of ketoconazole may result from perturbations in sterol or fatty acid metabolism or to accumulation of toxic endoperoxides secondary to its effect on oxidative and peroxidative systems. Overall, clinically evident side effects are infrequent when ketoconazole is used to treat vulvovaginal infections but, when present, gastrointestinal symptoms (in 5% of patients) and pruritus (in 2%) are the most common (37). Transient elevations of liver enzymes occur in about 10% of patients. In 281 patients undergoing treatment for vaginal candidiasis, van der Pas et al. (38) found side effects in 5% of patients (nausea 2%; headache 1%; epigastric pain, somnolence, and weakness, <1% each).

A ketoconazole dose of 200 mg twice a day for 5 days had an efficacy of approximately 90% for treating vaginal candidiasis (37,38). In two double-blind studies, ketoconazole (200 mg three times a day for 3 days) was as effective as

miconazole (400 mg intravaginal capsule three times a day for 3 days) at the initial evaluation 4 days after therapy. Relapse tended to occur more frequently in the ketoconazole group (37). However, in this comparative study, the optimal duration of therapy with ketoconazole was not used. Because of its potential hepatotoxicity and the availability of fluconazole (see later), ketoconazole has a limited role in treating genital candidiasis; it is used mainly for treatment or prevention of selected recurrent cases (17).

Another oral triazole, fluconazole, has had an important impact on therapy. Attractive characteristics of fluconazole are its long half-life, which makes it suitable as a single-dose treatment, and its apparent lack of serious systemic side effects. It may be less costly, and many patients prefer the convenience of a single, oral dose. Its efficacy is high but does not appear to be greater than that of topical agents in uncomplicated yeast vulvovaginitis. In a multicenter European noncomparative trial, a single dose of 150 mg was used in 180 patients (39). Short-term clinical response (assessed at 5 to 16 days) showed that 97% were cured or markedly improved. Longer-term response (at 27 to 62 days) showed 88% were cured clinically, with 73% cured mycologically. These rates are similar to those of topical therapies. Side effects, which were mainly mild gastrointestinal complaints, were reported as infrequent (8%). Abnormalities in laboratory test results occurred in approximately 10%, but all were minor and clinically insignificant. In a larger study of similar design, 952 patients were treated with the 150-mg single-dose regimen. Short-term response was similar to that noted earlier (95% either cured or improved). No longer-term responses were reported. Nine percent of patients reported adverse effects attributable (possibly or definitely) to fluconazole: mild gastrointestinal symptoms (4.8%), headache (1.2%), and dizziness (0.7%). These authors reported that of patients who had received previous topical treatment, 88% preferred the oral therapy, 10% preferred the intravaginal regimen, and 2% had no preference (40).

Both ketoconazole and fluconazole have the potential for clinically important interactions with other medications. These interactions are given in Box 1.

Box 1

Drugs with Clinically Important Interactions with Oral Ketoconazole or Fluconazole

Astemizole (Hismanal)

Calcium channel antagonists

Cisapride

Warfarin (Coumadin)

Cyclosporin A

Oral hypoglycemic agents

Phenytoin

Protease inhibitors

Tacrolimus

Terfenadine

Theophylline

Trimetrexate

Rifampin

From CDC 1998 guidelines for STD treatment

In a small but interesting blinded study, van Heusden et al. (41) measured efficacy, safety, and patient preference in 99 women randomized to 150 mg of fluconazole orally or a single dose of 1,200 mg of miconazole intravaginally. Short-term and long-term clinical and mycologic cure rates were not statistically different. Long-term cures (at 30 days) were excellent or good clinically in 88% of the fluconazole group and 76% of the miconazole group. Long-term mycologic cures were 73% for fluconazole and 82% for miconazole. There was no difference in the rate of rectal colonization after treatment. In this double-blind comparison, the authors were in a unique position to evaluate patient preference. At the longer-term visit, 43 patients stated the preferred the oral route, four preferred the vaginal route, and 46 had no preference.

Fluconazole persists in vaginal secretions longer than in plasma, and therapeutic vaginal concentrations are attained for up to 72 hours after the single 150-mg oral

dose. Minimal inhibitory concentrations for most *Candida* sp range from 0.4 to 0.8 µg/mL, whereas the concentration of fluconazole remains above 1 µg/mL in the vaginal secretions. Use of antifungal drugs has been reviewed (42). Single-dose fluconazole is a cost-effective treatment.

For treatment of vulvovaginal candidiasis in the nonpregnant patient, classification of patients into complicated versus uncomplicated is helpful (Table 12.4.) Patients with uncomplicated disorders may be treated with a short course of either oral or topical regimens. For patients with complicated disorders, either oral or topical regimens for 7 or more days are necessary. In these circumstances, we prefer to use fluconazole, such as 150 to 200 mg on days 1, 4, and 8. Some experts prefer to use topical therapy for most cases of vulvovaginal candidiasis, citing that there may be more prompt relief of symptoms due to the soothing application of the creams. On occasion, however, the topical application results in increased local symptoms, such as burning and irritation. Relief of these local symptoms may be achieved by application of low-potency topical corticosteroids; high-potency corticosteroids should be avoided as they may induce or exacerbate burning (43). Additional measures that may help relieve local symptoms include application of sitz baths with sodium bicarbonate. It also is noted that some of the older topical antifungal preparations, such as nystatin cream, may cause less local irritation.

Candidiasis may be more difficult to cure in pregnancy. No particular adverse effect in the mother or fetus was noted with miconazole or clotrimazole. The CDC treatment recommendations for pregnancy are limited to topical azoles, with most effective results reported with clotrimazole, miconazole, butoconazole, and terconazole. In pregnancy, many experts recommend 7 days of therapy (17).

A small percentage of yeast vaginitis is caused by *Candida* (formerly *Torulopsis*) *glabrata.* Infections due to *C. glabrata* are more likely to be characterized by burning, rather than itching, with little discharge and moderate edema. Filaments are not seen on KOH preparation, but clusters of round-to-ovoid spheres are present. In addition, *C. glabrata* infections are relatively refractory to imidazole compounds. However, use of 1% aqueous gentian violet provides quick and effective relief (in the absence of known allergy). Excess solution (forming a pool in the posterior fornix) should be absorbed on a fresh swab. The introitus and perianal area then should be “painted” with the solution and a minipad or panty liner provided. Because of staining of undergarments, inexpensive panties or liners are recommended for 72 hours.

The Wayne State University group also reported patients with recurrent *C. glabrata* infections who were unresponsive to usual therapies and noted that boric acid vaginal suppositories appeared to be of value (31). Sixty patients experienced 75 episodes of vaginitis attributed to *C. glabrata.* Of these patients, 40 had infection solely attributed to *C. glabrata* and 20 had mixed infection most commonly combined with BV. The initial treatment was vaginal boric acid 600 mg in a gelatin capsule daily for 14 days. Clinical improvement or cure occurred in 81% and mycological eradication was demonstrated in 77%. Because of the likelihood of recurrence, one third of patients received maintenance therapy with boric acid as 600-mg vaginal capsules administered twice weekly. The reported clinical and mycological response rates associated with topical and systemic azole therapy were less than 50% in all cases (44).

Candida tropicalis has not been generally recognized as a common isolate in yeast

vulvovaginitis, but Horowitz and colleagues (45) noted *C. tropicalis* in 23% (41/175) of women with yeast vaginitis. Recurrences were twice as common for *C. tropicalis* as for *C. albicans* (33 and 16%, respectively). These recurrent *C. tropicalis* cases were refractory to topical azoles, gentian violet, ketoconazole, and amphotericin cream.

Although failure of therapy and recurrence of vaginal yeast infections are common, there is poor understanding of this problem. Theories to explain recurrences are the intestinal "reservoir," sexual transmission, vaginal "relapse," and a candida-antigen immune deficiency. Resistance of yeasts, especially *C. albicans,* to antifungal drugs does not seem likely. Miles and coworkers (46) found 100% agreement between positive vaginal yeast cultures and positive stool cultures and suggested that therapy aimed at controlling the gastrointestinal reservoir of yeast might lead to improved results. In addition, vaginal and gut strains are the same in 67% of patients with simultaneous isolation. However, evidence against the intestinal reservoir theory is that chronic rectal carriers often have no vaginal infection and that neither short-term nor long-term oral therapy with nystatin has much effect in preventing recurrent vaginal infection (47,48). As noted earlier, sexual transmission as a mode of recurrence is supported by some, but not all, observations. According to the vaginal relapse theory, *Candida* is not eradicated from the vagina because of an intracellular phase or very low (i.e., nondetectable) colony counts. In the rat model, positive yeast cultures reappear 1 to 2 months after apparent cure (with negative vaginal and rectal cultures) in sexually inactive animals (47). Poor compliance is an unlikely explanation, especially with effective shorter regimens. Based on a depressed cell-mediated immunity observed in immunosuppressed patients with oral thresh, it has been speculated that there might be a deficiency in the lymphocytes that normally provide a vaginal host defense against mucosal invasion by *Candida* species. Studies of women with recurrent vulvovaginal candidiasis indicate that 40% to 70% exhibit candida-antigen–specific cutaneous anergy. These observations suggest that an acquired antigen-specific immunodeficiency in the vaginal epithelium makes the woman more susceptible to repeated episodes of vulvovaginal candidiasis after normal exposure to *Candida* organisms (49).

When a single course of therapy is unsuccessful, a second course of treatment with vaginal preparations sometimes is successful. Van Slyke et al. (29) noted that of ten patients who did not respond to nystatin, nine (90%) responded to boric acid. Also, of four patients who did not responded to a first course of boric acid, three (75%) responded to a second course.

Oral ketoconazole (in doses such as 400 mg daily for 5 days) leads to cures of approximately 75% 1 week after therapy and 50% 4 weeks after therapy in women with persistent disease (50). In a group of eight women who had persistent yeast vaginitis after 5 days of oral ketoconazole, treatment with 400 mg daily for 10 days led to cure in all at 1 week and in 80% at 4 weeks.

Maintenance ketoconazole (100 mg daily) in women with frequent recurrences (defined as at least four episodes in 12 months before entry) was effective at suppressing clinical recurrences (51). However, there is little carryover effect, and the patients encounter a small risk of hepatotoxicity. Alternatives for prevention of recurrent vulvovaginal candidiasis are shown in Box 2. Risks of suppressive therapy must be weighed against the benefits.

Box 2

Treatment and Prevention of Recurrent Vulvovaginal Candidiasis[a]

Step 1: Eradication Regimen

For example: fluconazole 150 mg p.o. on days 1, 4, and 8

or

Intravaginal azoles for 10–14 days

or

Ketoconazole 400 mg daily for 14 days

Step 2: Prevention Regimen for 3–6 months

For example: fluconazole 150 mg p.o. weekly

or

Ketoconazole 100 mg p.o. daily

or

Itraconazole 100 mg p.o. every other day

or

Clotrimazole 500 mg vaginally weekly

or

Any topical azole, applied daily

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[a]Recurrent candidiasis usually is defined as ³ 4 episodes per year.
Based on CDC 1998 STD treatment guidelines; Sobel JD. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. *Clin Infect Dis* 1992;14[Suppl 1]:S148–S153; and Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000;30:662–678.

Recent CDC guidelines note that optimal treatment for recurrent infection has not been established (17). Before initiating maintenance regimens, the CDC guidelines recommend confirmation by culture. Any predisposing factors should be eliminated,

but this nearly always must be done by the patient herself. Although recurrent yeast infection has been a common presenting complaint in women with HIV infection, the vast majority of women with recurrent yeast infection do not have HIV infection. Accordingly, the CDC advises that routine performance of HIV testing for women with recurrent yeast vulvovaginitis and without other risk factors is unwarranted (17).

Strategies to prevent symptomatic infection in the general population (i.e., those not having frequent symptomatic infections) have not been developed. In contrast to recommendations for *T. vaginalis,* the recommendations for prevention of yeast vulvovaginitis do *not* include routine treatment of either the sexual partner or of asymptomatic women colonized with yeasts.

Neither yeast vulvovaginitis nor asymptomatic yeast colonization has been associated with adverse pregnancy outcome, postoperative infection, or salpingitis.

Optimal treatment of recurrent yeast vulvovaginitis in women with HIV infection has not been determined. It is recommended that HIV-infected women be managed the same way as non–HIV-infected women with recurrent infection (17).

BACTERIAL VAGINOSIS

Important information has continued to develop regarding BV (formerly known as *Gardnerella vaginalis* vaginitis, *Haemophilus vaginalis* vaginitis, and “nonspecific vaginitis”), including its etiology, epidemiology, treatment, and sequelae.

In 1955, Gardner and Dukes (1) described a clinical syndrome of vaginitis having the following features: a gray (85% of cases), homogenous, odorous discharge with a pH of 5.0 to 5.5, without yeast forms or trichomonads. The volume of discharge was moderate; upon examination of a wet mount, there were characteristic stippled or granulated epithelial cells called “clue cells.” Leukocytes were not prominent. The vaginal secretions were frothy in one fourth of patients. In the vaginal secretions of patients, *H. vaginalis* (subsequently called *Corynebacterium vaginale* and now named *G. vaginalis*) was isolated, but it was not isolated from any normal patients. Gardner and Dukes called this specific infection *H. vaginalis* vaginitis, suggesting this term in preference to “nonspecific vaginitis,” a designation that had been applied previously. Reports largely confirmed the association between *G. vaginalis* and the characteristic syndrome, although this organism also is recovered from a considerable percentage of asymptomatic women (52).

It now is clear that BV results from a shift in bacteria from the normal peroxide-producing lactobacilli to a polymicrobial group (in high concentrations) consisting of anaerobes (*Bacteroides* sp, *Peptostreptococcus* sp, and *Mobiluncus* sp), *G. vaginalis,* and *Mycoplasma hominis*. *Gardnerella vaginalis* has been found in 45% to 98% of cultures from women with BV and in 16% to 48% of normal control women; anaerobic Gram-negative rods in 53% to 76% of BV cases and in 0% to 41% of controls; *Peptostreptococcus* in 29% to 63% of BV cases and in 5% to 27% of controls; *M. hominis* in 58% to 76% of BV cases and in 20% of controls; and *Mobiluncus* sp in 51% of BV cases and in 0% on controls; whereas lactobacilli have generally been found in 9% to 38% of BV cases and in 68% to 90% of controls (53). In a series of reports elucidating the role of peroxidase-producing facultative lactobacilli, investigators in Seattle found these organisms in 96% (27/28) of women

with normal secretions and in only 6% (4/67) of women with BV. On the other hand, anaerobic lactobacilli, which do not produce peroxidase, were more common in cases of BV (36% vs. 4% in normals; $p < 0.001$) (54). Taken together, these studies make a strong argument for an important role of peroxidase-producing lactobacilli in the protection of normal vaginal flora, particularly by the presence of peroxidase and a halide ion (Table 12.6) (55,56).

Normal Vaginal Secretions	Bacterial Vaginosis
pH 4.0–4.4	pH ≥4.7
10^8 CFU/mL	Up to 10^{11} CFU/mL
Lactobacilli predominate	Few lactobacilli
	Abundant anaerobes, Gardnerella vaginalis, and genital mycoplasmas

TABLE 12.6. SCHEMATIC REPRESENTATION OF MICROBIAL SHIFTS IN BACTERIAL VAGINOSIS

Bacterial vaginosis now is recognized as a very common entity. Although lack of standardized diagnostic criteria has limited epidemiologic studies, it has been estimated that BV occurs in perhaps 15% of private gynecology patients, 10% to 30% of pregnant women, and 5% to 25% of college students (17,57). In STD clinics, the prevalence has ranged from 12% to 61%. Between one third and three fourths of women with BV have no attributable symptoms. Bacterial vaginosis has been associated with nonwhite race, but no mechanism is evident to explain this relationship. Some evidence links BV with IUD use, but the relationship of previous pregnancy and sexual activity varies from study to study. All authorities agree that BV is not exclusively an STD.

The chief symptom is vaginal discharge rather than pruritus. Some patients may note an offensive vaginal odor, which may be accentuated after coitus. Upon examination, the typical discharge, characterized as whitish, creamy or milky, and homogeneous (compared with normal secretions, which are heterogeneous or floccular), often is evident at the introitus. Vulvovaginal irritation is less marked than with trichomoniasis or candidiasis.

Table 12.2 summarizes the characteristics of BV and normal vaginal secretions. The diagnosis of BV should be based on the general characteristics of volume, color, adherence, and viscosity and on specific features of high pH, “amine” odor with KOH, homogeneous consistency, and presence of clue cells. True clue cells are epithelial cells that are so heavily stippled with bacteria that the borders are obscured; epithelial cells with few bacteria and clear borders should *not* be identified as clue cells.

Clinically, the diagnosis of BV should be based on the presence of three of the following four criteria: (i) a homogeneous, milky or creamy, noninflammatory discharge that adheres to the vaginal walls, (ii) presence of true clue cells on microscopic examination, (iii) pH of secretions above 4.5, and (iv) a fishy or amine odor with or without the addition of 10% KOH (Box 3).

Box 3

Clinical Criteria for Diagnosis of Bacterial Vaginosis

Presence of three of the following four criteria is necessary for diagnosis:

- Homogeneous, milky or creamy discharge
- Presence of true clue cells on microscopic examination
- pH of secretions above 4.5
- Fishy or amine odor with or without addition of 10% KOH

From CDC 1998 guidelines for STD treatment

Despite the likely role of anaerobes, there is no need to culture for them, and there is no diagnostic value in culturing for *G. vaginalis* in vaginal secretions. Such expensive testing adds unnecessarily to the cost of diagnosis.

Gram staining of vaginal secretions may be used to diagnose BV (Fig. 12.2 and Fig. 12.3) (58). Specimens from patients with BV have numerous mixed bacteria and a paucity of lactobacilli. Clue cells may be seen clearly. In comparison, patients with normal secretions have fewer bacteria, which are predominantly lactobacilli cell types. There are a considerable number of patients with an intermediate type of flora on Gram stain. These patients seem to be developing BV or perhaps resolving it spontaneously. Using the Gram stain, investigators noted that the three bacterial morphotypes that were most reliable in establishing a diagnosis of BV were lactobacilli seen as large Gram-positive rods; *Gardnerella* and *Bacteroides* sp seen as small Gram-negative or Gram-variable rods; and *Mobiluncus* sp seen as curved Gram-negative or Gram-variable rods (59,60).

These morphotypes have been used to establish a 10-point BV score, where 0–3 is normal, 4–6 is intermediate, and 7–10 is BV (61). This scoring system has acceptable interobserver variability after some training and experience of the slide reader. Hillier and colleagues (59) studied these three patterns of vaginal Gram stains over 6 to 11 weeks in 762 pregnant women. Initially, 65% were read as normal, 16% as intermediate, and 19% as BV. At follow-up, 81% of women with normal flora remained normal. Of those women with intermediate flora, 32% acquired BV and 30% shifted to normal flora. Only 12% of women with BV initially shifted to normal (59).

Other proposed diagnostic tests include the Pap smear (61), oligonucleotide probes, and detection of amines, short-chain volatile acids (such as putrescine, cadaverine, and trimethylamine), and enzymes (such as proline aminopeptidase) (60).

Standardized criteria have not been routinely applied to the Pap smear for diagnosis of BV; BV should be diagnosed on the basis of vaginal, not cervical, secretions (62). Because poorly performed wet mounts can lead to misdiagnosis in up to one third of women, Hillier (60) notes that the vaginal Gram stain is preferred. The Gram-stained smears have good-to-excellent sensitivity (62%–100%) and a good-to-excellent positive predictive value (76%–100%) (63,64). However, we recognize that few offices are equipped to do Gram stains, and very few practitioners have had training in reading BV from a Gram stain.

Because of the variability in interpretation of the wet mount, a number of new diagnostic tests for BV have become available or are anticipated to be released shortly. One technique includes a nucleic acid probe for high concentrations of *G. vaginalis.* This firm VPIII Microbial Identification Test (Becton Dixon & Co., Sparks, MD) has a reported sensitivity of 95% to 97% for women meeting clinical criteria for BV, and specificity ranges from 71% to 98% (65). A second diagnostic approach recently approved by the FDA is the Fem Exam pH and Amines Test Card (Litmus Concepts Inc., Santa Clair, CA). This card has two indicators, one for pH ³4.7 and one for the presence of amines at a high concentration. The card is color indicated and easy to read. If vaginal pH ³4.7, the pH portion of the card forms a “+” sign. Similarly, when the amine concentration is above the threshold, another “+” sign appears in the amine test portion. Presence of both a positive pH and positive amine test form the basis for a strong presumptive diagnosis of BV. The Fem Exam pH and Amines Test Card had a sensitivity of 86% and a specificity of 92% compared to the clinical criteria. The positive predictive value was 79% and the negative predictive value was 95%. It should be noted that this Fem Exam Card addresses only two of the four criteria recommended by the CDC. Thus, these two tests should be combined with a clinical description of the discharge and microscopic examination. In circumstances where microscopy is not readily available, then this card can be combined solely with clinical description of the discharge. The performance of this card test needs evaluation in everyday clinical settings.

Before the late 1970s, treatment for BV was directed at *G. vaginalis* with sulfa creams, ampicillin, or tetracycline. However, Pheifer et al. (66) reported poor responses with all of these agents, whereas with metronidazole (500 mg twice a day orally for 7 days) the cure rate was approximately 90% (66). In three later double-blind studies, metronidazole or tinidazole was confirmed to be highly effective. Balsdon et al. (67) compared metronidazole (400 mg twice a day for 7 days), oxytetracycline (500 mg twice a day for 7 days), and placebo (twice a day for 7 days). Patients whose randomized therapy had failed then were treated with metronidazole. Altogether, 16 of 17 patients treated with metronidazole were clinically cured, and cultures of *G. vaginalis* became negative in 15, even though metronidazole has no *in vitro* activity. Oxytetracycline therapy led to clinical cure in six of ten patients, and the placebo led to clinical cure in only one of nine patients. In a larger double-blind study, Malouf et al. (68) found that metronidazole was curative in 91% of 22 patients, whereas sulfa cream, doxycycline, and ampicillin were curative in 55% of 18, 64% of 33, and 48% of 23 patients, respectively. Piot et al. (69) carried out a double-blind comparison of oral tinidazole (which has a longer half-life than metronidazole) to vaginal cream, with or without sulfonamides. At 1 week, tinidazole had cured 29 (97%) of 30 patients, whereas the oral placebo plus vaginal creams had cured 16 (60%) of 27. It was suggested that cream containing sulfonamide was not more effective than the cream itself. In view of potential side effects, some had advised treating this mild infection with ampicillin orally, at first

(70).

New effective regimens have been developed (Table 12.7). Oral clindamycin 300 mg twice daily for 7 days results in a clinical cure rate of over 90%. In a comparative study with oral metronidazole for 7 days, the corresponding cure rates were 94% for clindamycin and 96% for metronidazole. Adverse reactions occurred in 11% of patients taking clindamycin and 15% of those taking metronidazole, but none of these side effects (mostly gastrointestinal) resulted in discontinuation of the medications (71,72).

TABLE 12.7. CENTERS FOR DISEASE CONTROL AND PREVENTION RECOMMENDED REGIMENS FOR TREATMENT OF BACTERIAL VAGINOSIS IN NONPREGNANT WOMEN

Single-dose metronidazole (2 g) may be used to treat BV, especially when compliance with the 7-day regimen may be poor. However, the efficacy of the single-dose regimen is slightly lower. Based on four randomized trials, the overall cure rate with the 7-day regimen is 95% and that of the single-dose regimen is 84% (17). In a meta-analysis, Lugo-Mira and coworkers (73) reported somewhat different estimates of cure rates: 72% for single-dose treatment and 78% for 7-day treatment. These differences were not significant (73).

Bacterial vaginosis also may be treated with a 3-day clindamycin regimen, given as 100 mg ovules intravaginally. Compared to oral metronidazole (500 mg twice a day for 7 days), the clindamycin ovules were equivalent (both had cure rates of 67%–68%). There were no significant differences in adverse effects (74).

In previous editions of this textbook, it was noted that metronidazole should be avoided in the first trimester. A recent meta-analysis does not indicate teratogenicity of metronidazole in humans. As noted in the 1998 STD treatment guidelines, some health care providers prefer the intravaginal route for application of metronidazole because of the lack of systemic side effects and because mean peak serum concentrations of metronidazole after intravaginal application are less than 2% of the levels achieved with a standard 500-mg oral dose. The 1998 STD treatment guidelines no longer carry the warning to avoid use of metronidazole in the first

trimester of pregnancy (Table 12.8).

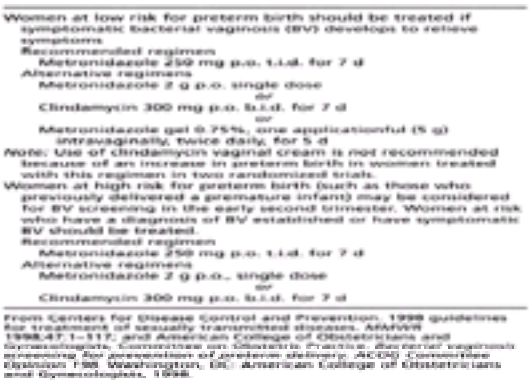
Women at low risk for preterm birth should be treated if symptomatic bacterial vaginosis (BV) develops to relieve symptoms
Recommended regimen
Metronidazole 250 mg p.o. t.i.d. for 7 d
Alternative regimens
Metronidazole 2 g p.o. single dose
or
Clindamycin 300 mg p.o. b.i.d. for 7 d
or
Metronidazole gel 0.75%, one applicationful (5 g) intravaginally, twice daily, for 5 d
Note: Use of clindamycin vaginal cream is not recommended because of an increase in preterm birth in women treated with this regimen in two randomized trials.
Women at high risk for preterm birth (such as those who previously delivered a premature infant) may be considered for BV screening in the early second trimester. Women at risk who have a diagnosis of BV established or have symptomatic BV should be treated.
Recommended regimen
Metronidazole 250 mg p.o. t.i.d. for 7 d
Alternative regimens
Metronidazole 2 g p.o., single dose
or
Clindamycin 300 mg p.o. b.i.d. for 7 d
From Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47:1–117; and American College of Obstetricians and Gynecologists, Committee on Obstetric Practice. Bacterial vaginosis screening for prevention of preterm delivery. ACOG Committee Opinion 198. Washington, DC: American College of Obstetricians and Gynecologists, 1998.

TABLE 12.8. RECOMMENDED REGIMEN FOR TREATING BACTERIAL VAGINOSIS IN PREGNANT WOMEN

Persons with HIV infection should be treated with the same regimens as persons without HIV (17).

Currently, there are no effective strategies for prevention of BV.

Bacterial vaginosis has been associated with several complications of pregnancy and surgery. As discussed in Chapter 18, there is strong evidence linking BV to intraamniotic infection (75). As discussed in Chapter 19, there are several studies associating BV and preterm birth. In a review, McGregor (76) noted that BV was strongly associated with preterm PROM, with risk ratios from 1.3 to 7.3. Bacterial vaginosis microorganisms have been found to produce proteases that can facilitate transport of bacteria to fetal membranes and impair membrane integrity in experimental models. In a treatment trial in patients with BV in pregnancy, 372 women at 16 to 26 weeks were randomized to either 2% clindamycin cream or placebo. There was no significant difference in birthweight, low birthweight rate, PROM, amnionitis, or neonatal sepsis (77). Other recent trials using oral therapy for BV in pregnancy have demonstrated improvement in outcome, but only in high-risk patients. Recommendations regarding treatment of asymptomatic BV in pregnancy for the purpose of improving outcome are addressed in Chapter 19.Although BV may be a treatable cause of preterm delivery, present data are still preliminary. A statement from the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice indicated that it would be appropriate to adopt the following strategies for screening and treatment of BV after the first trimester. (i) Screening for BV may be considered in women at high risk for preterm labor, on the basis of having delivered a preterm infant herself, having had a low prepregnancy weight of less than 50 kg, or both. (ii) Women who have positive test results or symptoms of BV should be treated with metronidazole administered orally. Vaginal treatment appears not to be as effective in preventing preterm labor. (iii) Studies do not clarify whether women who test positive and are treated or those who test negative should be rescreened periodically during pregnancy. In addition, the effect of re-treatment of persistent or recurrent BV is unclear. (iv) Routine BV screening of

asymptomatic women at low risk for preterm birth and the subsequent treatment of women with positive results cannot be endorsed based on current studies (78). Goldenberg et al. (79) noted that trials of prenatal treatment of BV for prevention of preterm birth have met with mixed results (79). They conclude that the results suggested in women with a previous preterm delivery and with BV diagnosed in the second trimester, treatment for 1 week or more with oral metronidazole, and perhaps with erythromycin, has resulted in a significant reduction in the incidence of preterm delivery. They note, however, that when antibiotics have been administered vaginally, when the antibiotic course has been shorter than 1 week, when antibiotics not including metronidazole have been used, or women at low risk have been treated, no significant reduction in preterm delivery has been observed. As noted in Chapter 19, we concur that screening for BV in pregnancy should be limited to patients at highest risk (such as women with previous preterm birth themselves); screening should take place in the early second trimester; and an oral regimen such as metronidazole for 7 days should be used (79).

Recent studies have associated BV with first-trimester and second-trimester pregnancy loss, but clinical implications are not clear, as intervention trials have not been performed (80,81 and 82). Soper et al. (83,84) have reviewed the relationship between BV and postoperative infections. Although preliminary data suggest that BV increases the risk of postpartum (85) and postoperative infections, the effectiveness of antenatal or preoperative treatment of BV has not been assessed for prevention of these infections (84). Bacterial vaginosis also has been associated with pelvic inflammatory disease (86). However, in 1992, Larsson and coworkers (87) reported that treatment of BV (oral metronidazole 500 mg three times daily for 10 days vs. placebo) prior to first-trimester abortion significantly reduced postabortion PID. Of 174 evaluated women, PID developed in 3.6% (3/84) in the metronidazole group and 12.2% (11/90) in the placebo group ($p < 0.05$). Further studies on preoperative treatment are awaited.

DESQUAMATIVE INFLAMMATORY VAGINITIS

Although desquamative inflammatory vaginitis was first described nearly 50 years ago, this entity has not been well studied nor widely recognized. As shown in Box 4, the diagnosis of desquamative inflammatory vaginitis is based upon the presence of a heavy, often frothy discharge, an elevated pH, and a purulent vaginitis with mild vaginal erythema.

Box 4

Characteristics of Desquamative Inflammatory Vaginitis
Diagnosis

- Heavy, often frothy discharge
- pH >4.5
- Purulent vaginitis with vaginal erythema
- Wet mounts: abundant coccoid bacteria (rare to no lactobacilli); large numbers of polymorphonuclear leukocytes and parabasal cells, but no clue cells

Differential diagnosis

- Atrophic vaginitis
- Trichomoniasis
- Erosive lichen planus
- Cervicitis
- Foreign body
- Cervical or vaginal cancer (with secondary necrosis and exudate)
- ▪Bacterial vaginosis

Treatment

- Clindamycin vaginal cream 2%
- In estrogen-deficient women, replacement therapy may help, especially when there is relapse.

Wet mounts are diagnostic and show large numbers of polymorphonuclear leukocytes and parabasal cells, but no clue cells. In addition, there are few lactobacilli in the background bacteria, but there are abundant coccoid bacilli. Cultures are generally not helpful in delineating etiology or therapy. The differential diagnosis of desquamative inflammatory vaginitis is extensive. Because of the outpouring of white blood cells, trichomoniasis must be ruled out, and the laboratory picture often looks like atrophic vaginitis. In any patient who has abundant white blood cells, cervical origin (from cervicitis) must be considered. The presence of foreign bodies must be determined, as well as necrosis and exudate secondary to a vaginal or cervical cancer. The dermatologic condition of erosive lichen planus also enters into the diagnosis. Although there is not much overlap in the clinical picture between desquamative inflammatory vaginitis and BV, both entities have an elevated pH and a complaint of a discharge.

Most observers have identified a good response to clindamycin vaginal cream when used in a usual course, but relapse is common. In postmenopausal or other estrogen-deficient women, supplemental hormone replacement therapy may be helpful, especially when there is relapse. Figure 12.4 shows a typical wet mount in a patient with desquamative inflammatory vaginitis (88,89).

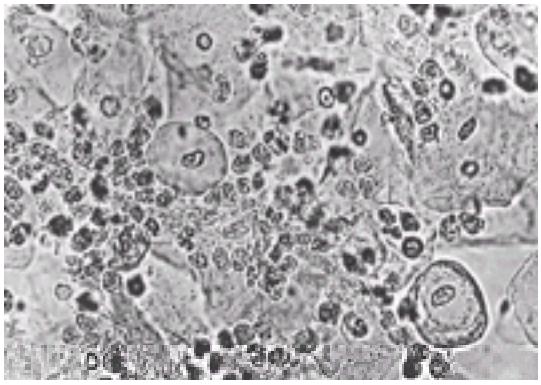

FIGURE 12.4. Wet-mount findings in desquamative inflammatory vaginitis. Note the abundant polymorphonuclear leukocytes and parabasal cells. (Courtesy Paavonen J. *J Infect Dis Obstet* 1996;4:257)

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13

POSTABORTION INFECTION, BACTEREMIA, AND SEPTIC SHOCK

POSTABORTION INFECTION

In the last 20 years, medical and legal decisions have changed the practice and outcome of pregnancy termination (Fig. 13.1 and Fig. 13.2). Death and major complications from abortion have decreased across the country (1), but death from abortion is still a problem, with infection the fourth leading cause (Fig. 13.3) (2). Among deaths after spontaneous abortion, infection was responsible for 48%; among deaths after illegal abortion, infection was responsible for 65% (3). From 1972–1978 to 1979–1985, the rate of infection as a cause of death after legal abortion decreased. In the former period, infection was responsible for 24% of deaths (n = 34, the leading cause); in the latter period, infection was responsible for 14% (n = 10, the fourth leading cause). It is particularly gratifying that deaths from legal abortion were reduced by 50% overall, and deaths due to infection were reduced by 70% (Table 13.1) (4,5,6 and 7). Fever and infection also were among the leading causes of nonlethal complications after legal abortion (8). Among 42,548 women undergoing abortion, 4,303 (10%) experience some complication. Pelvic infection was diagnosed in 436 (1%), infection and hemorrhage in 307 (0.7%), and fever in only 865 (2%) (2).

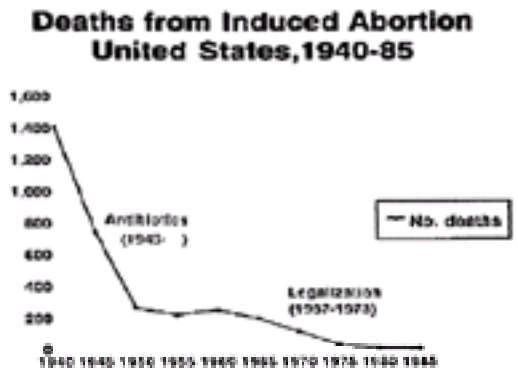


FIGURE 13.1. Deaths from induced abortion in the United States, 1940 to 1985. (Data from Council in Scientific Affairs, American Medical Association. Induced termination of pregnancy before and after Roe v. Wade. Trends in mortality and morbidity of women. *JAMA* 1992;268:3231–3239.)

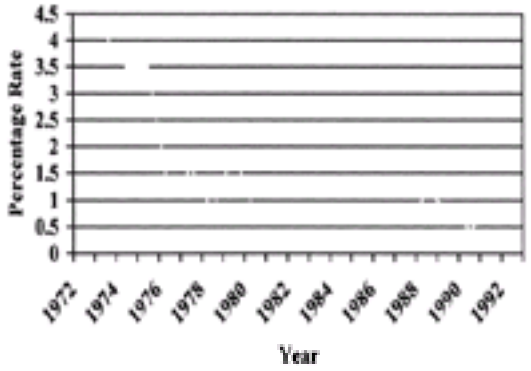


FIGURE 13.2. Case fatality rate* for legal abortions in the United States, by year from 1972 to 1992. *Legal induced abortion-related deaths per 100,000 legal induced abortions. (From Centers for Disease Control and Prevention. Abortion surveillance–United States, 1996. *MMWR* 1999;48:16.)

FIGURE 13.3. Major complications of legal abortion in the United States, 1970 to 1990. Major complications include unintended surgery, transfusion administered, hospital stay longer than 10 days, or temperature greater than 38°C for more than 3 days. (Data from Council in Scientific Affairs, American Medical Association. Induced termination of pregnancy before and after Roe v. Wade. Trends in mortality and morbidity of women. *JAMA* 1992;268:3231–3239.)

	No. of Deaths (%)	
Cause of Death	1972–1978	1979–1985
Hemorrhage	27 (19)	16 (22)
Infection	34 (24)	10 (14)
Embolism	34 (24)	11 (15)
Anesthesia	22 (16)	21 (29)
Other	24 (17)	14 (19)
Total	141 (100)	72 (100)

From Council in Scientific Affairs, American Medical Association. Induced termination of pregnancy before and after Roe v. Wade, trends in mortality and morbidity of women. *JAMA* 1992;268: 3231–3239.

TABLE 13.1. CAUSES OF DEATH FROM LEGAL ABORTION UNITED STATES, 1972–1985

Risk factors for death after legal abortion are advancing gestational age, advancing maternal age, “black and other” race, and method used (with the lowest risk accompanying procedures used at early gestational ages) (7).

As with death after legal abortion, risk factors for complications after abortion are longer duration of pregnancy and technical difficulties. At less than 9 weeks the major complication rate was two of 1,000 procedures; at 13 to 14 weeks the rate was six of 1,000; and at more than 20 weeks the rate was 15 of 1,000 in the most recent national data set (7). Earlier data showed that for suction curettage in the first trimester, major complications were least frequent (<0.5%), as was risk of death (1.3/100,000 abortions) (8). For intrauterine injections, the major complication rate was higher (2%), and the risk of death was nine times greater (12.5/100,000). For either hysterotomy or hysterectomy, the risk of death (41.3/100,000) was 32 times greater than for curettage (8). Because of the increased risk of complications with injection techniques for second-trimester termination, interest has developed in suction curettage for mid-trimester procedures. Curettage of these pregnancies was found to be associated with significantly fewer- complications in the hands of experienced operators (using laminaria and special instruments) (9).

Pathophysiology

Infection after abortion is an ascending process that occurs more commonly in the

presence of retained products of conception or operative trauma (Fig 13.4). Perforation of the uterus may be followed by severe infection, whether or not there is bowel trauma (10,11). Infection frequently follows hysterotomy, because there is necrosis, foreign body (suture material), and blood clot in the thick uterine incision, contamination from the lower genital flora and, often, poor drainage of the uterine cavity.

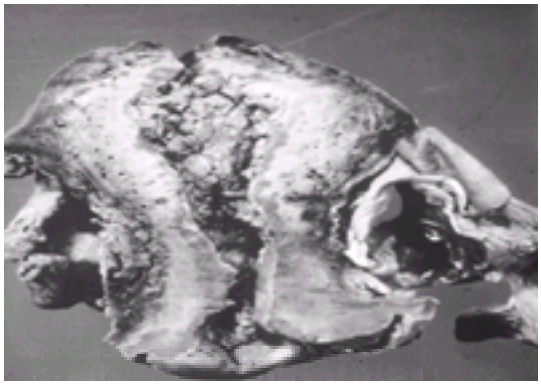


FIGURE 13.4. Uterus removed at autopsy from lethal septic abortion. Note retained products of conception and site of uterine perfuration at fundus.

Diagnosis

For patients who have had an abortion, the diagnosis of postabortion infection often is readily made. Symptoms may include fever, chills, malaise, abdominal pain, and vaginal bleeding, perhaps with passage of placental tissue. Postoperative infection may be more difficult to diagnose in patients who have illegal abortions because of patient denial of the procedure. Septic abortion should be considered in every woman with lower abdominal pain, especially in the presence of fever and vaginal bleeding.

Physical findings may include elevated temperature, tachycardia, and tachypnea. Because bacteremia occurs more commonly with infected abortion than with other pelvic infections, shock may arise from sepsis as well as from blood loss. In the presence of sepsis, the patient may appear agitated, toxic, or disoriented. Usually there is lower abdominal tenderness. On pelvic examination, there often is blood and perhaps a foul odor in the vagina. It is important to look for cervical and vaginal lacerations, especially in a suspected illegal abortion. The cervix is most often open and will readily admit a sponge forceps. If a catheter from an illegal abortion is still in the cervix, it should *not* be removed immediately, because radiographic techniques can be used to rule out perforation.

On bimanual examination, uterine tenderness often is noted, and parametrial cellulitis or abscess may be detected. Rarely, gas gangrene of the uterus may be detected by crepitation in the pelvis.

Laboratory diagnostic evaluation should include complete blood count, urinalysis, culture and Gram stain of cervical material, two sets of blood cultures, anteroposterior roentgenogram of the abdomen and pelvis, and upright chest x-ray film. Free hemoglobin may be noted in the serum or in the urine in infections caused by *Clostridium perfringens* or other organisms with hematotoxins. Gram stain of cervical exudate may reveal the predominant organism immediately. Results of blood cultures commonly are positive in septic abortion. This yield is much greater than that with other pelvic infections. Roentgenograms in patients with suspected illegal abortions help rule out a foreign body or free air under the diaphragm resulting from perforation. Gas in the uterus is a late sign of uterine gangrene and commonly does not develop at all. Ultrasound examination may be used as the initial imaging technique, as it is likely to detect retained placental tissue, foreign body, and possibly air in the pelvic structures. Blood should be obtained for typing and potential cross-matching.

Prevention

Prevention of infected abortion consists mainly of avoiding unplanned pregnancies by access to, and proper use of, contraceptives. Because infection is less common after legal abortion than after illegal abortion, an additional important means to prevent postabortion infection is to provide access to all women to early, safe, legal abortion. Technical considerations include avoiding perforation and incomplete abortions during curettage procedures. Hysterotomy is accompanied by so large an increase in risk that it is rarely, if ever, indicated. Hysterectomy for abortion and sterilization is best reserved for women with additional uterine conditions.

Treatment

The essentials of treating infected abortion are (a) supportive therapy including replacement of blood and fluids; (b) surgical removal of any infected tissue; and (c) appropriate antibiotic therapy. After proper diagnostic studies have been carried out, vigorous parenteral antibiotic therapy should be administered. Because of the likelihood of multiple organisms and bacteremia in septic abortion, broad-spectrum antibiotic therapy such as clindamycin plus gentamicin is appropriate for initial therapy. For the patient in septic shock, addition of penicillin G or ampicillin is advisable.

After antibiotic therapy is initiated, surgical drainage is essential unless there is confidence that infection is confined to the endometrium and there is no retained placental tissue. Prompt curettage usually suffices. In experienced hands and with special instruments, the uterus may be safely evacuated transcervically up to 20 to 24 weeks, with ultrasound guidance. Delaying evaluation of the uterus because of the patient's poor condition is a mistake in management that may prove fatal (12).

When the uterus is too large for an operator to undertake suction curettage, high-dose oxytocin administration often is successful. Rather than increasing the dose of oxytocin stepwise, we start with 300 mU/min of oxytocin in normal saline (0.9%) or in Ringer's solution. At this dose, oxytocin exerts an antidiuretic effect. To avoid water intoxication, see Box 1.

Box 1

Measures to Avoid Water Intoxication in Patients Receiving High-Dose Oxytocin

1. Administer the oxytocin in an electrolyte solution (not in 5% dextrose)
2. Avoid administration of electrolyte-free solution via other intravenous catheters
3. Observe closely for decrease in urine output
4. Determine serum sodium concentration, if symptoms arise. One recommended regimen is to give 50 U in 500 mL of saline over 3 hours (approximately 300 mU/min), followed by a 1-hour rest. The regimen is repeated, each time increasing the amount of oxytocin by 50 U per 500 mL of saline, until the fetus aborts or a total dose of 300 U of oxytocin in 500 mL is reached.

Use of prostaglandin E_2 (PGE_2) suppositories is contraindicated in the presence of sepsis, because it causes fever. Stubblefield and Grimes (12) recommended 15-methyl prostaglandin F_{2a} (carboprost tromethamine) 250 µg intramuscularly every 2 to 3 hours. If none of these drugs is available, a large Foley catheter (50-mL balloon) may be placed in the lower uterus (12).

In a few situations, laparotomy may be indicated to control infection. Indications for exploratory laparotomy are shown in Box 2.

Box 2

Indications for Exploratory Laparotomy in Cases of Infected Abortion

1. Failure to respond to curettage and appropriate medical therapy
2. Perforation and infection with suspected bowel injury
3. Pelvic or adnexal abscess
4. Poor response to vigorous medical therapy and debridement techniques
5. Gas gangrene (clostridial necrotizing myometritis)

It must be emphasized that the mere isolation of *Clostridium* sp from the pelvis does not necessarily signify life-threatening infection or the need for laparotomy. Instead, the initial treatment for a patient with presumed clostridial infection is penicillin in large doses, curettage, and supportive therapy. A pelvic roentgenogram should be obtained because it may reveal myometrial gas, but this occurs late, if at all. If there is no response or deterioration, laparotomy is indicated.

Prognosis

The overall outlook for a patient with infected abortion is good, but this condition

must still be considered a life-threatening infection. In the United States from 1972 to 1978, 339 women died of abortion complications, many from infection. From 1979 to 1985, there were a total of 123 abortion-related deaths. A total of only five deaths from illegal abortion were reported to the Centers for Disease Control and Prevention [CDC] from 1978 to 1985. Since 1980, the death to case ratio has been less than one per 100,000 abortions (13). The case fatality rate for legal abortion in the United States from 1972 to 1992 is shown in Fig. 13.2. As noted earlier, both death and major complications have decreased dramatically in this period. Reasons for these improvements in outcome are improvement in physician skills; introduction of improved methods (suction curettage); and availability of safe, early, and legal abortion (7).

Reproductive potential after an infected abortion may be compromised by Asherman syndrome, pelvic adhesions, or incompetent cervix. However, the CDC concluded that vacuum aspiration overall does not adversely affect fecundity, but that dilation and evacuation for second-trimester termination increases the risk of subsequent spontaneous abortion, prematurity, and low-birthweight infants (7).

BACTEREMIA

The principal pathogens responsible for bacteremia in obstetric-gynecologic patients are coliform organisms, particularly *Escherichia coli;* group B streptococci; anaerobic streptococci; and *Bacteroides* sp (14). Other significant causative organisms include *Clostridium* sp, enterococci, and, rarely, *Staphylococcus aureus* and *Streptococcus pneumoniae.* Multiple aerobic and anaerobic organisms may be responsible for bacteremia in certain patients. The reported overall incidence of bacteremia is about 7.0 per 1,000 obstetric-gynecologic admissions (14).

Most obstetric-gynecologic patients with bacteremia respond promptly to intravenous antibiotic therapy, and their prognosis is better than that of medical patients with bacteremia. Blanco and colleagues (14) were unable to discern any difference in outcome when they compared bacteremic obstetric patients and nonbacteremic obstetric patients with similar infections. However, septic shock develops occasionally, with an appreciable mortality rate.

Recognizing that antibiotic use often is inappropriate (22%–64% of the time in recent reviews) and that inappropriate antibiotic use is accompanied by adverse results, standards of treatment for bacteremia have been published (15). Input was provided by the Infectious Diseases Society for Obstetrics and Gynecology. These standards are given in Table 13.2.

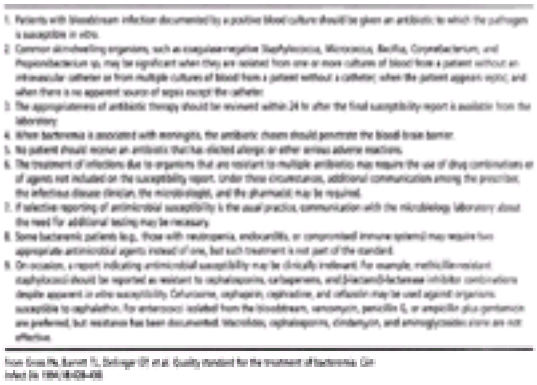


TABLE 13.2. QUALITY STANDARD FOR THE TREATMENT OF BACTEREMIA

SEPSIS, SEPTIC SHOCK, AND THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Dramatic progress has been made in our understanding of the pathophysiology of the human response to serious infection, but this knowledge has not translated into improved outcome. Terms such as sepsis, septic shock, and septicemia have not been used precisely (16). We must consider current terminology, as shown in Table 13.3 and Table 13.4. Only a small percentage of infected obstetric-gynecologic patients are bacteremic (in nearly all series, <10% of patients with infection). An even smaller percentage, probably less than 2% to 5% of these women, develop sepsis. Approximately half of all patients with sepsis have bacteremia. Sepsis has been defined as a subset of patients with systemic inflammatory response syndrome. About 15% of all patients with systemic inflammatory response syndrome do not have infection but rather other precipitating causes, such as trauma or pancreatitis. Sepsis has been graded by several authors (Table 13.3), for example, as severe or as early versus refractory. Sepsis, sepsis syndrome, and septic shock can be thought of as a continuum. Authorities have suggested that older terms, such as septicemia, warm shock, and cold shock, be abandoned (16).

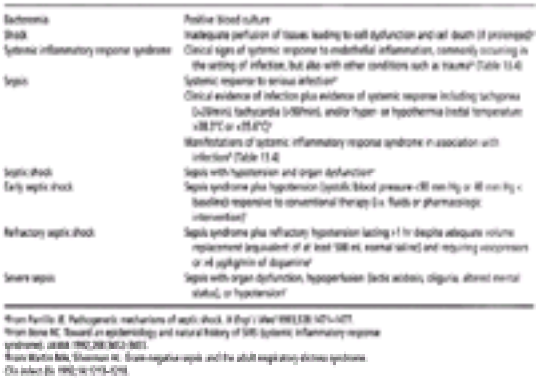


TABLE 13.3. RECENT DEFINITIONS OF TERMS USED IN DESCRIBING SEPSIS

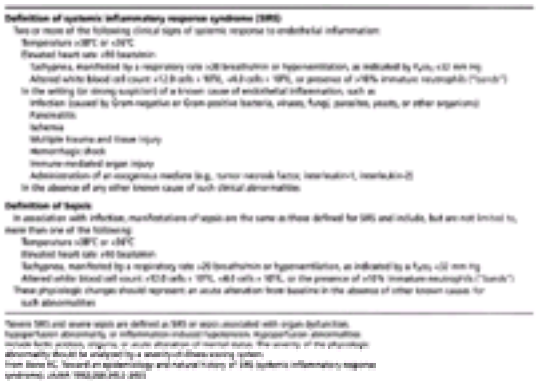


TABLE 13.4. DEFINITIONS OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME[a] AND SEPSIS

Predisposing Factors

All patients in shock suffer from decreased tissue perfusion. Sepsis is the third most common cause of shock in the general hospital population, exceeded by acute hemorrhage and myocardial infarction.

Although any organism can cause septic shock, the principal offenders are the endotoxin-producing aerobic Gram-negative bacilli. In most clinical series, Gram-negative bacteria are implicated in approximately 60% to 80% of septic shock cases; Gram-positive bacteria in 5% to 25%; and mixed or fungal infections in 4% to 16%. The organism is not identified in about 10% of cases of septic shock (17).

The microorganisms responsible for sepsis may be endogenous or acquired during hospitalization. Risk factors for septic shock include advanced age, chronic debilitating diseases, disseminated malignancies, and immune deficiency disorders. Patients receiving immunosuppressive drugs, cytotoxic agents, and parenteral hyperalimentation also are at increased risk. Surgical procedures in the biliary, urinary, intestinal, and genital tracts clearly predispose the patient to increased risk of septicemia. In older animal models, investigators found that pregnancy increased susceptibility to the effects of endotoxin.

The prognosis for survival is affected by the patient's underlying medical illness. In selected series, the mortality associated with bacteremia alone is 40%. If clinical septic shock develops, the proportion of fatalities increases to 35% to 45% (18). In a study of 270 patients with Gram-negative bacteremia, Freid and Vosti (19) emphasized the grave prognosis of sepsis in patients with serious underlying diseases. Patients with “rapidly fatal,” “non-fatal,” and “no underlying fatal” diseases had observed fatality ratios of 86%, 46%, and 16%, respectively (19). The vast

majority of obstetric patients with septic shock would be included in the category of “no underlying fatal disease.” In such patients, Freid and Vosti showed that prognosis is adversely affected by imprecise initial medical and surgical therapy. Successful management of septic shock requires an understanding of its pathophysiology and appropriate therapy.

Pathophysiology Of Sepsis

Several reviews have characterized the pathophysiology of sepsis (Table 13.5) (17,18,20,21,22,23,24 and 25).

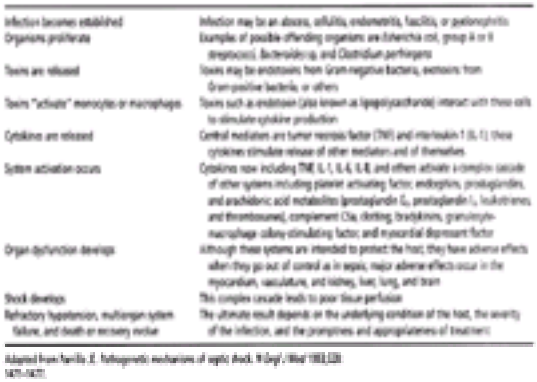


TABLE 13.5. PATHOPHYSIOLOGIC EVENTS IN SEPTIC SHOCK

Endotoxin is a complex lipopolysaccharide present in the cell walls of Gram-negative bacteria. The critical component of endotoxin is a substituent termed lipid A, which has a b-1-6-diglucosamine backbone joined in an ester and amide linkage to long-chain fatty acids. Endotoxin is released into the host's circulation upon bacterial cell disruption and initiates an intricate series of derangements in Gram-negative infections. Still, a considerable percentage (up to 25% or greater) of cases of sepsis are caused by other organisms that elaborate different kinds of toxins. Therapies focusing on blocking the effects of endotoxin can only be of benefit in Gram-negative infections.

It has been shown dramatically in animal models that the cytokines play key mediating roles in sepsis, with tumor necrosis factor alpha (TNF-a) and interleukin-1 (IL-1) being central mediators in the cascade (Fig. 13.5). Cytokines also play an essential role in the defense against infection, such as by up-regulating the cytolytic activity of lymphocytes and the expression of complement receptors; activating macro phages; enhancing the oxidative burst of leukocytes; and stimulating B-cell and T-cell proliferation. Although this improved understanding has opened new opportunities for therapy, it is wise to note that blocking the cytokines may interfere with the body's attempts to control infection and thus may lead to adverse sequelae, as reported in animal models (17).

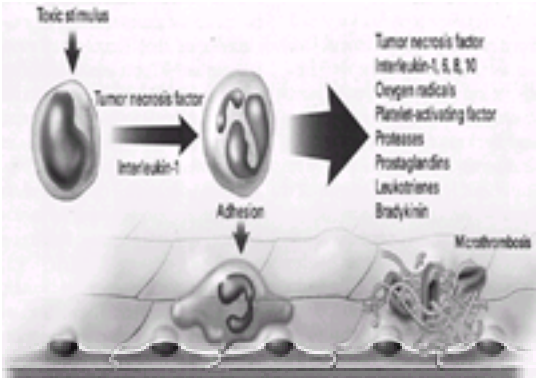


FIGURE 13.5. Early biomedical events in sepsis. An initial toxic stimulus (e.g., endotoxin) triggers the production of proinflammatory monokines (e.g., tumor necrosis factor and interleukin-1). These cytokines, in turn, result in neutrophil–endothelial-cell adhesion, activation of clotting, and generation of numerous secondary inflammatory mediators, including other cytokines, prostaglandins, leukotrienes, and proteases. Antiinflammatory compounds, such as interleukin-6 and interleukin-10, which may serve as negative feedback to the inflammatory process also are released. (From Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Eng J Med* 1999;340:207–214.)

Perhaps the key target organ in sepsis is the heart, mediated through myocardial depressant factor. Table 13.6 shows the cardiovascular characteristics, which can be summarized in the acute phase as hypotension, high output, low vascular resistance, and low ejection fraction (20).

Cardiovascular Measure	Acute Phase—Hypotension and Decreased Systemic Vascular Resistance	Recovery Phase—Normotension
Mean arterial pressure (mm Hg)	Low (40)	nl (75)
Central venous pressure (mm Hg)	Low (2)	nl (5)
Cardiac output (L/min)	High (7 l)	nl (5)
Stroke volume (mL)	nl (75)	nl (75)
Systemic vascular resistance (dyne·sec·cm⁻⁵)	Low (270)	nl (1,100)
Ejection fraction (% of end-diastolic volume ejected with each beat)	Low (33)	nl (60)
End-diastolic/end-systolic ventricular volume (mL)	High (diastolic = 225/systolic = 150)	Nl (diastolic = 125/systolic = 50)

Numbers in parentheses are representative values.
Adapted from Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med* 1993;328:1471–1477.

TABLE 13.6. CARDIOVASCULAR MEASURES IN SEPTIC SHOCK

A common and serious consequence of sepsis is adult respiratory distress syndrome (ARDS). About 25% of patients with Gram-negative sepsis develop ARDS, which in the presence of sepsis has a mortality of 60% to 90% (16). Endotoxin is the proximal mediator and may cause direct lung injury, but endotoxin mainly acts through

mediators such as the cytokines, complement, and arachidonic acid metabolites. These factors act in concert with leukocytes and platelets to cause impairment of the endothelium, increased capillary permeability, migration of neutrophils, edema, decreased lung compliance, and refractory hypoxia (16). The topic was reviewed in detail by Ware and Matthay (26).

Endothelial injury may adversely affect the kidneys, liver, brain, clotting mechanisms, and central nervous system, giving rise to the full-blown picture of sepsis and multiorgan failure.

Clinical Manifestations

One of the earliest manifestations of septic shock is alteration in the patient's sensorium, including combativeness, anxiety, confusion, disorientation, and impaired intellect and judgment. Other early signs of evolving septicemia include temperature instability, flushing, and peripheral vasodilation. Diminished blood flow leads to myocardial impairment, manifested by tachycardia, arrhythmia, and myocardial ischemia, perhaps with infarction and biventricular failure.

Approximately 25% to 50% of patients with septic shock develop evidence of ARDS, the most frequent manifestations of which are tachypnea, dyspnea, stridor, cyanosis, lobar consolidation, and pulmonary edema. In the obstetric-gynecologic patient with septic shock, the abdominopelvic examination is critically important. There may be evidence of intestinal obstruction, wound infection, evisceration, peritonitis, or pelvic abscess.

Other pertinent clinical manifestations include oliguria or anuria, hematuria or pyuria, jaundice, nausea, and vomiting. Development of a coagulopathy may be heralded by spontaneous hemorrhage from the gastrointestinal or genitourinary tract and bleeding from venipuncture sites.

Diagnosis

In the different diagnosis of septic shock, the most important element is hypovolemic shock. Much less common causes in obstetric-gynecologic patients are acute pulmonary embolus, amniotic fluid embolus, cardiogenic shock, cardiac tamponade, dissection of the aorta, hemorrhagic pancreatitis, and diabetic ketoacidosis. Appropriate laboratory studies are listed in Table 13.7.

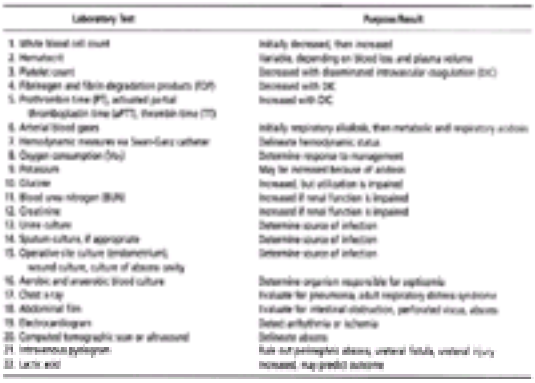


TABLE 13.7. LABORATORY STUDIES IN SEPTIC SHOCK

In the early stage of septic shock, the white blood cell count may be low but almost invariably rises, with a marked shift to the left. Because acute blood loss may commonly accompany sepsis, the hematocrit may be elevated because of the decreased effective circulating plasma volume resulting from pooling in the capillary bed. Diminished platelet count, decreased fibrinogen level, and elevated level of fibrin degradation products are the earliest and most sensitive indicators of disseminated intravascular coagulation.

In the early stage of septic shock, the patient may have a transient respiratory alkalosis due to endotoxin-induced hyperventilation, but it is quickly superseded by severe metabolic acidosis, which commonly complicates the situation. Lactic acid is the major organic acid responsible for metabolic acidosis. Lactate levels correspond to the severity of circulatory failure in shock. Patients with the highest levels of lactate have the worse prognosis for ultimate survival.

In patients with concurrent ARDS, respiratory failure leads to a superimposed respiratory acidosis, and this *acute* state will be manifested by decreased arterial pH, serum bicarbonate, and arterial Po_2, and increased arterial Pco_2. Serum potassium concentrations may increase as intracellular potassium flows from the cell in exchange for hydrogen ion.

With marked decrease in renal blood flow, urine output will first diminish and then cease. Creatinine clearance will decrease, and serum concentrations of substances normally handled by the kidney, such as urea, creatinine, and uric acid, then will increase.

Plasma glucose levels in septic shock usually are normal or high. In the early stage of septic shock, when cardiac output is high and peripheral resistance is low, both plasma glucose and plasma insulin levels are elevated. Despite the presence of high concentrations of insulin, however, glucose uptake by peripheral cells is impaired, reflecting a state of at least partial insulin antagonism.

Microbiologic studies are essential in confirming the diagnosis of septic shock and determining the origin of infection. A sample of urine should be obtained aseptically through the urethral catheter for microscopic examination and bacteriologic culture. Sputum culture and Gram stain should be performed in patients with pulmonary findings or symptoms. At least two sets of blood cultures should be obtained to determine the pathogenic organism responsible for septicemia. Blood specimens should be evaluated for fungi, especially in patients receiving parenteral hyperalimentation and those receiving immunosuppressive drugs. Finally, cultures of the operative site wound or abscess cavity should be obtained when appropriate.

Selected radiographic procedures may be helpful in the evaluation of the patient with septic shock. Posteroanterior and lateral films of the chest may indicate whether a primary respiratory infection is present and may permit early detection of septic

pulmonary emboli, cardiomegaly, pulmonary edema, or ARDS. Immediate recognition of the pulmonary changes associated with ARDS is essential because the disorder has such an adverse effect on the prognosis in septic shock. These radiographic changes may develop after clinical changes of ARDS already are apparent.

Abdominal films should be obtained if there is suspicion of intestinal obstruction, perforated viscus, foreign body, or abdominopelvic abscess. Computerized axial tomography and ultrasonography may be helpful in delineating an abscess, particularly in obese patients in whom pelvic examination alone is difficult. Excretory urography may be indicated when there is a need to establish the presence or absence of perinephric abscess, ruptured renal pelvis, ureteral fistula, or operative ureteral injury.

Accurate monitoring of cardiovascular performance is of paramount importance in the patient with septic shock (27). Standard electrocardiography should be used to detect myocardial ischemia or arrhythmias. Finally, Swan-Ganz monitoring may provide essential data in assessing the adequacy of venous return and determining pulmonary artery systolic and diastolic pressures, pulmonary vascular resistance, pulmonary capillary wedge pressure, and cardiac output.

Management

Patients with septic shock are acutely ill and require admission to an intensive care unit at the earliest possible moment. The general approach to therapy traditionally has been twofold: support the organ systems and eradicate infection. From a theoretical viewpoint, another objective may now be listed: blockade of the effects of sepsis mediators. The objectives and goals of therapy are summarized in Table 13.8, and some specifics are listed in Table 13.9.

Objective	Goal of Treatment
Correct metabolic abnormalities and restore organ function	Correct hypotension; restore mean arterial pressure to at least 60 mm Hg; pulmonary artery wedge pressure to 14–18 mm Hg; maintain adequate oxygenation
	Correct tissue hypoperfusion; restore hemoglobin to >10 g/dL; oxygen saturation to >92%; blood lactate concentrations to normal; cardiac index to ≥2.2 L/min/m² in nonseptic shock and >4.0 in septic shock
	Correct organ dysfunction; restore renal (blood urea nitrogen, creatinine, output), hepatic (bilirubin), pulmonary (alveolar-arterial gradient), cardiovascular (MAP, cardiac index), and central nervous system (mental status) measures to normal; transfer to intensive care unit
Eradicate infection	With appropriate antibiotic therapy and surgical intervention, definitively treat source of sepsis
Block effects of mediators of the sepsis cascade	This approach remains experimental. Block or reverse the adverse effects of these mediators.

MAP, mean arterial pressure.

TABLE 13.8. GENERAL APPROACH TO THERAPY OF SEPTIC SHOCK

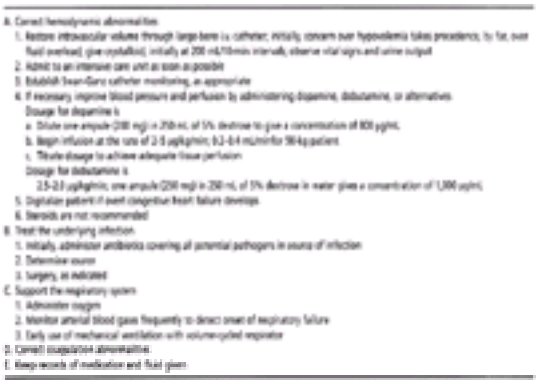


TABLE 13.9. SOME SPECIFICS IN TREATMENT OF SEPTIC SHOCK IN OBSTETRICS AND GYNECOLOGY

Correction of Hypotension and Hypoperfusion

The first priority in treating septic shock is correction of hemodynamic abnormalities. The immediate goal of therapy is to restore the patient's effective circulating blood volume. A large-bore intravenous catheter should be inserted. If the patient has experienced acute blood loss, this objective should be accomplished by administering either packed red cells or whole blood. In the absence of blood loss, plasma volume loss initially may be corrected by infusion of isotonic crystalloids, such as normal saline or lactated Ringer's solution, or colloid solutions, such as Plasmanate or albumin. Fluid resuscitation should be started, even before a Swan-Ganz catheter is inserted. In women without cardiac or respiratory signs, initial fluid replacement should be administered at 200 mL per 10-minute interval. Whether the patient presents in a hemodynamic or hypodynamic situation, immediate fluid replacement is essential. Fluid overload is rarely acute and should not concern the clinician to the point that fluid resuscitation is compromised (27). Adjustments can be made later based on blood pressure, pulse, jugular venous pulse, urine output, and Swan-Ganz catheter readings.

An arterial line may be inserted to provide continuous assessment of both blood pressure and arterial oxygenation, and a urethral catheter should be placed to monitor urine output.

Continued restoration of intravascular volume generally can be guided by measurements of the patient's pulmonary artery wedge pressure, which should be maintained at a level of 14 to 18 mm Hg. Lower levels do not provide adequate filling pressures for the left atrium and left ventricle, and higher levels may overload the cardiovascular system. As Peitzman and colleagues (27) noted, however, assessment of initial wedge pressure alone may not accurately predict the response to volume infusion in septic patients because there may be a discrepancy between wedge pressure on the one hand and left atrial pressure and ventricular function on the other hand. Accordingly, cardiac output and ventricular function studies should be measured, as well as wedge pressure.

Some investigators propose that oxygen consumption (VO_2) is the critical endpoint to follow during fluid resuscitation in septic or other critically ill patients (27). A low VO_2 is a poor prognostic sign, as it usually occurs after hemodynamic deterioration. On the other hand, an increase in VO_2 may be a reliable indicator of appropriate volume replacement (27).

Intravenous fluid administration should include glucose solutions. To avoid low oncotic pressure, approximately one third of the fluid volume should be given as protein solution. Serum potassium levels should be checked regularly.

Two well-designed trials concluded that high-dose corticosteroid therapy did not provide any benefit in septic shock (28,29).

P>The most common cause of death in septic shock is respiratory failure due to ARDS (26). The major objective in the management of the critically ill patient is *prevention* of respiratory failure. Because patients with septicemia and shock are hypoxic and acidotic, oxygen by nasal cannula or face mask should be instituted immediately. 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 hypoxic damage to the pulmonary vasculature.

Coagulation abnormalities should be identified promptly and corrected by administration of cryoprecipitate, fresh frozen plasma, fresh whole blood, or platelets in patients with disrupted circulation. Only rarely should it be necessary to consider use of heparin for management of a consumption coagulopathy.

Some patients will respond to fluid resuscitation, but addition of an inotropic agent may improve hemodynamic function at a lower wedge pressure (27). Dopamine and dobutamine both are effective (30). In low doses (0.5–3 µg/kg/min), dopamine causes dilation of renal and mesenteric arteries (27). At doses of 5 to 12 µg/kg/min, dopamine has a weak b-mimetic effect on the heart, increasing myocardial contractility and heart rate without causing a disproportionate increase in myocardial oxygen consumption. Unlike pure b-stimulants, dopamine causes vasoconstriction in skeletal muscle. Its net effect is to preserve renal, splanchnic, coronary, and cerebral blood flow.

These actions of dopamine are dose dependent. In doses exceeding 15 to 20 µg/kg/min, the principal effect of dopamine is stimulation of a-receptors with resultant vasoconstriction, an effect noted with older vasopressors such as metaraminol and ephedrine. The ultimate result of this vasoconstriction is a transient increase in cardiac output followed by a sustained decrease in tissue perfusion, which is clearly an undesirable effect in shock.

Dopamine should be administered by continuous intravenous infusion through a central line. The solution for infusion can be prepared by mixing one 5-mL ampule (200 mg/ampule) in 250 mL of 5% dextrose (D5W). Dopamine should not be mixed with bicarbonate solution because dopamine is inactivated in alkaline medium. The concentration of dopamine will be 800 µg/mL. The recommended starting dose for

intravenous infusion is 2 to 5 µg/kg/min. For a 50-kg woman, the initial dose would be approximately 0.2 to 0.4 mL/min. The infusion should be titrated upward to obtain the desired blood pressure and organ perfusion.

The corresponding initial dose of dobutamine is 2.5 to 20 µg/kg/min. One ampule (250 mg) diluted in 250 mL of D5W gives a concentration of 1,000 µg/mL. See Box 3 for other regimens.

Box 3

Drugs Commonly Used for Circulatory Support

Drug	Pharmacologic Role	Clinical Effect	Usual Dose Range
Epinephrine	a- and b-Adrenergic agonist	Chronotropism, inotropism, vasoconstriction	5–20 µg/min
Norepinephrine	a- and b-Adrenergic agonist[a]	Chronotropism, inotropism, vasoconstriction	5–20 µg/min
Dopamine	Dopamine and b-adrenergic agonist, progressive a-adrenergic effect with increasing doses	Chronotropism, inotropism, vasoconstriction	2–20 µg/kg body weight/min
Dobutamine	b-Adrenergic agonist	Chronotropism, inotropism, vasodilation	5–15 µg/kg/min
Phenylephrine	a-Adrenergic agonist	Vasoconstriction	2–20 µg/min

[a]The a-adrenergic effect is greater than the b-adrenergic effect.
From Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999;340:207–214, with permission.

In patients with overt congestive heart failure complicating septic shock, digitalization is indicated. This can be accomplished by administering a loading dose of 0.75 mg of digoxin in three divided doses, 4 to 6 hours apart, followed by a daily maintenance dose calculated to provide a serum digoxin level of 0.5 to 2.5 ng/mL. Dosage of digoxin must be adjusted in the presence of impaired renal function; usual maintenance doses range from 0.125 to 0.375 mg/day.

Eradication of Infection

As hemodynamic parameters are being corrected, attention also must be directed toward eliminating the underlying source of infection. Treatment of life-threatening septicemia requires administration of broad-spectrum antibiotics. Although it is not the only acceptable regimen, the antibiotic combination of penicillin (5 million units every 6 hours) or ampicillin (2 g intravenously every 6 hours), tobramycin or gentamicin (initially 1.5 mg/kg every 8 hours with dosage adjustment based upon

antibiotic levels), and clindamycin (900 mg every 6 hours) or metronidazole (15 mg/kg initially, followed by 7.5 mg/kg every 6–8 hours) will provide effective coverage against pelvic pathogens. Aminoglycoside dose may need adjustment on the basis of serum levels (31). Therapy with this or another appropriate antibiotic combinations should be initiated promptly after cultures have been obtained. In patients who have diarrhea initially or who develop this symptom, metronidazole, cefoxitin, or chloramphenicol can be used in place of clindamycin.

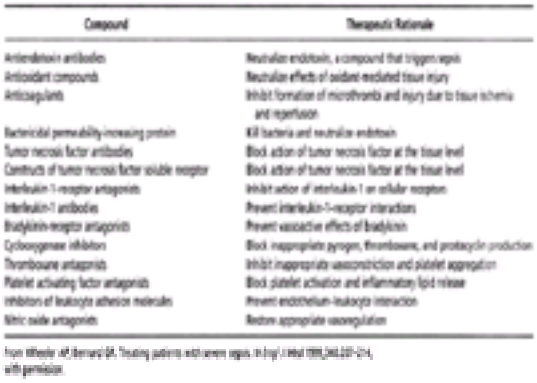
In certain unique situations, the obstetrician may need to use different antibiotic combinations. For example, immunosuppressed patients with neutropenia may require carbenicillin or ticarcillin in conjunction with amikacin to treat infections due to resistant *Pseudomonas* organisms. Antifungal agents, such as amphotericin or miconazole, may be necessary to eliminate fungal septicemia in patients receiving parenteral hyperalimentation or in immunosuppressed patients. A semisynthetic penicillin should be substituted for aqueous penicillin G when *S. aureus* is suspected or actually isolated.

Elimination of the source of infection commonly requires surgery. Definitive surgical therapy should not be delayed simply because the patient's blood pressure and tissue perfusion respond initially to fluid resuscitation. Surgery in the presence of deteriorating maternal cardiovascular function, although hazardous, often is necessary to remove the focus of infection. Delay may prove fatal. Most investigators recommend endotracheal intubation and general anesthesia for emergency abdominal delivery, particularly in a patient with hemodynamic abnormalities.

The preferred agents for general anesthesia are those that produce the least depressive effect on the cardiovascular system of the mother and fetus. Inhalation gases that result in marked uterine relaxation, such as halothane, should be avoided in patients with chorioamnionitis and septic shock, because such patients already are particularly susceptible to uterine atony and postoperative hemorrhage. One anesthetic regimen that has been widely advocated for emergency cesarean section is the combination of thiopental, nitrous oxide, and oxygen. In addition, succinylcholine is given concurrently to facilitate intubation. In selected instances, cyclopropane and ketamine also may be used for anesthesia in unstable hypotensive patients because these two drugs tend to minimize cardiovascular depression.

Blockade Of Mediators

Improved understanding of the pathophysiology of septic shock has prompted a series of new therapeutic approaches aimed at interrupting the effects of endotoxin or the cytokine mediators. These therapies are summarized in Table 13.10. Despite study of thousands of patients and expenditure of huge sums of money, these new approaches have been disappointing, as none has shown efficacy in decreasing mortality overall (32). However, in retrospectively defined subgroups, benefit has been demonstrable, such as in those with high mortality. It seems evident that dramatic improvement in mortality will not be achieved by an approach aimed at a single point in the sepsis cascade. Because of the central roles of TNF and IL-1, it has been suggested that combination therapies may be of greater benefit.



Compound	Therapeutic Rationale
Antiendotoxin antibodies	Neutralize endotoxin, a compound that triggers sepsis
Antioxidant compounds	Neutralize effects of oxidant-mediated tissue injury
Anticoagulants	Inhibit formation of microthrombi and injury due to tissue ischemia and reperfusion
Bactericidal permeability-increasing protein	Kill bacteria and neutralize endotoxin
Tumor necrosis factor antibodies	Block action of tumor necrosis factor at the tissue level
Constructs of tumor necrosis factor soluble receptor	Block action of tumor necrosis factor at the tissue level
Interleukin-1-receptor antagonists	Inhibit action of interleukin-1 on cellular receptors
Interleukin-1 antibodies	Prevent interleukin-1–receptor interactions
Bradykinin-receptor antagonists	Prevent vasoactive effects of bradykinin
Cyclooxygenase inhibitors	Block inappropriate pyrogen, thromboxane, and prostacyclin production
Thromboxane antagonists	Inhibit inappropriate vasoconstriction and platelet aggregation
Platelet activating factor antagonists	Block platelet activation and inflammatory lipid release
Inhibitors of leukocyte adhesion molecules	Prevent endothelium-leukocyte interaction
Nitric oxide antagonists	Restore appropriate vasoregulation

From Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999;340:207–214, with permission.

TABLE 13.10. INVESTIGATIONAL TREATMENTS OF SEPSIS

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14

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is described by the Centers for Disease Control and Prevention (CDC) as a spectrum of upper genital tract inflammatory disorders, which includes any combination of endometritis, salpingitis, tuboovarian abscess, and pelvic peritonitis (1). In general, acute PID refers to an infection of the upper genital tract that is attributed to the upward spread of microorganisms from the vagina and endocervix to the endometrium, fallopian tubes, or contiguous structures. Although the terms *acute PID* and *acute salpingitis* are often used interchangeably, salpingitis is the most important component of the PID spectrum. The term *chronic PID* is generally used inappropriately. By definition, PID is an acute infectious process. *Chronic* refers to the sequelae of the acute process such as adhesions, scarring, and tubal obstruction.

PID is one of the most frequent and important infections seen in nonpregnant

reproductive-age women. It is associated with major clinical and public health problems, including diagnosis, treatment, prevention, sequelae, health care costs, and morbidity and mortality.

In women, the epidemic of sexually transmitted diseases (STDs) has been associated with a secondary epidemic of acute PID and ultimately with a tertiary epidemic of sequelae such as tubal infertility and ectopic pregnancies. Eschenbach (2) particularly reported that PID is the most common serious infection in women and causes approximately 30% of infertility cases, 50% of ectopic pregnancies, and many cases of chronic pelvic pain. Not only is acute PID the most common important complication of sexually transmitted pathogens for women, but PID is also the major medical and economic consequence of STDs in young women (4).

EPIDEMIOLOGY

Precise figures on the incidence and prevalence of acute PID in the United States are not available. Because PID is not a reportable disease in many areas, various sources have been used to estimate these data, including patient surveys, hospital discharge rates, private physician office visits, emergency room visits, retrospective self-reporting, and extrapolations from incidence figures of gonorrhea and chlamydia. This situation is further complicated by the wide spectrum of clinical presentation and lack of accurate clinical diagnostic criteria associated with acute PID. In addition, it has been estimated that up to two thirds of cases of PID go unrecognized (4).

During the 1970s and 1980s, as a result of the STD epidemic and the widespread use of the intrauterine contraceptive device, the incidence of acute PID increased (5,6,7,8,9,10 and 11). In that era, approximately 1 million women were diagnosed annually with PID (10,11) and the estimated yearly cost was $5.5 billion (12,13). A large part of this cost is attributed to long-term sequelae of PID, such as tubal factor infertility (TFI) and ectopic pregnancy. In the 1980s, 250,000 to 300,000 women were hospitalized each year with a diagnosis of salpingitis or PID (8,9). During this time, more than 1.2 million visits for PID to private physician offices occurred, of which approximately 420,000 were an initial visit for PID (9). In addition, an estimated 150,000 surgical procedures were performed annually for complications of acute PID (8,10). In the late 1980s, an estimated 30% of patients with acute PID were hospitalized (14). However, whereas in 1982, 14.2% of U.S. women, aged 15 to 44 years, reported receiving treatment for PID, by 1988, only 10.8% so reported (15).

Since the peak in the early 1980s, hospitalization rates for acute PID have declined (Fig. 14.1). Rolfs et al. (11) reported that although hospitalization rates for acute PID declined in the 1980s, office visit rates remained relatively unchanged. Among various age-groups, the smallest decrease in hospitalization rates occurred in the 15- to 19-year-old age-group, which was 10%, compared with the 40% decrease seen in the 20- to 24-year-old group. As a result of this pattern, the 15- to 19-year-old age-group had the highest hospitalization rate without adjusting for sexual activity (16). For 1990, Washington and Katz (12) estimated 200,000 hospitalized patients with PID, with an additional 1,277,000 outpatient cases. These authors included an estimate for PID cases seen in clinics and emergency departments as well as physician offices (ratio, 2:1), thereby resulting in the greater estimate of ambulatory cases.

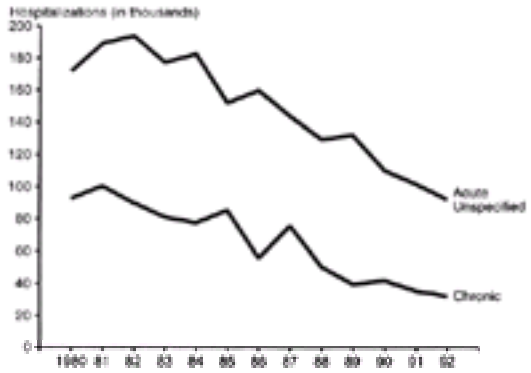


FIGURE 14.1. Rates of hospitalization for pelvic inflammatory disease among women aged 15 to 44 years: United States, 1980–1992.

More recently, the CDC reported on the trends in the incidence of PID from 1981 to 1996 (17). Using estimates from the National Hospital Discharge Survey, National Hospital Ambulatory Care Medical Care Survey, and the National Ambulatory Medical Care Survey, the CDC reported that the number of hospitalized cases of PID declined by 57% from 1981 (289,086) through 1996 (113,903). On the other hand, the number of new visits for PID diagnosed in physician offices showed no significant change (283,375 cases in 1981 and 285,000 cases in 1996). An additional 379,000 cases of PID on average were diagnosed annually in emergency departments and outpatient clinics from 1992 to 1996. Thus, approximately 780,000 cases of acute PID are being diagnosed annually in the United States as we enter the new millennium. As a result of the decrease in the number of PID cases and the change to less-expensive ambulatory treatment, Rein et al. (17) recently estimated that the direct medical cost for PID and its sequelae in 1998 was $1.88 billion.

Several suggestions have been put forth in an attempt to explain the apparent decrease in the number of PID cases being seen in the United States. During the same time, a parallel decrease in the incidence of gonorrhea has occurred in the 1980s (4). More recently, in some local areas, a decrease in chlamydial infection has been seen (18,19 and 20). This decline has been implicated in the decrease in the estimated number of PID cases. During the 1980s, there was a significant decline in the use of intrauterine devices (IUDs) as a method of contraception in the United States and an effort to increase use of barrier methods and oral contraceptives in the high-risk sexually active young age-group (14 to 24 years old). In addition, two economic factors may have played a role in producing an apparent but not true decline in the incidence of PID. The increasing penetration of managed care, particularly closed staff Health Maintenance Organizations (HMOs), may have shifted patients from private physician offices (which are surveyed) to clinics (which are not) and has probably emphasized ambulatory treatment over hospitalization for PID. The second factor relates to the economics of the past decade, with increasing poverty and lack of health insurance coverage resulting in lack of access to health care and increasing use of public sector clinics not included in national survey data.

Westrom and Eschenbach (4) noted that the incidence of PID is influenced by multiple factors, including (a) prevalence of STDs; (b) demography (nulliparous,

single, divorced, or widowed women have higher incidence than parous or married women; (c) economics; (d) health care characteristics of the population; (e) sexual attitudes; (f) douching; (g) smoking and drug habits; and (h) contraceptive practices.

Increasing attention has recently focused on what Wolner-Hanssen et al. (21) called "silent" or "atypical" PID. This term was used for the condition in which women with documented infertility, secondary to tubal scarring and adhesions, provided no past history of PID despite the fact that the scarring suggested that pelvic infection had occurred in an asymptomatic or unrecognized form. Rather than a totally asymptomatic, silent infection, this "unrecognized" form of PID is an atypical clinical presentation (e.g., with intermenstrual bleeding and mucopurulent discharge) that is not recognized or diagnosed as PID. Unrecognized PID is probably as common, if not more common, than clinically apparent disease.

To prevent the significant economic and medical sequelae of PID, we must develop methods of prevention and treatment that are based on the microbiologic etiology of the disease. Unfortunately, several major problems complicate the attempt to elucidate this etiology. Among these are the facts that first, the clinical criteria for diagnosis are vaguely defined and have not been standardized among the various studies in the literature. Second, the fallopian tubes, which are the site of infection, are inaccessible for routine microbiologic studies. Third, the microbiologic methodology used in many of the investigations has focused on the sexually transmitted pathogens *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and has not attempted to recover all the potential organisms that may be responsible for acute PID, such as *C. trachomatis,* anaerobic bacteria, facultative bacteria, viral agents such as herpes simplex virus (HSV) and cytomegalovirus (CMV), or possibly genital tract mycoplasmas.

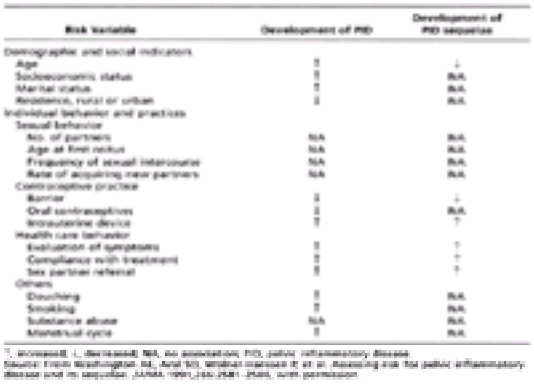
Knowledge of the risk factors, pathogenesis, and therapeutic response, both immediate and long-term, is also required if we are to prevent the significant economic impact and sequelae of PID. The effectiveness of such an effort has been demonstrated in Sweden, where a dramatic decrease of approximately 50% occurred in the incidence of acute PID from 1977 to the mid-1980s (22). Westrom (22) associated this decrease with routine efforts to diagnose chlamydia, examine and treat male partners of women with PID, and decrease the use of IUDs by women younger than 25 years, coupled with the increased usage of oral contraceptives.

RISK FACTORS

The CDC (9) and Washington et al. (23) have emphasized the importance of risk assessment in the management and prevention of PID. Risk assessment is dependent on an understanding of known and suspected risk factors or risk markers. A risk factor is a variable that has a direct casual effect. On the other hand, a risk marker has an indirect effect and may be a surrogate for a risk factor. However, clinically, both risk factors and risk markers are useful predictors of risk (23). As noted by Padian et al. (24), factors associated with the development of disease can be assessed in relation to (a) increased risk of exposure to an infectious organism or organisms; (b) risk of acquiring an infection after exposure; (c) risk of developing disease when infected; and (d) risk of progression to sequelae. Washington et al. (23) suggested that among the determinants of risk for PID are (a) inoculum size of pathogenic organisms, (b) number of infecting organisms, (c) virulence of infecting organisms, (d) host suspectivity, and (e) environmental factors. For the purpose of

clinical risk assessment, it is the latter two variables that need to be addressed.

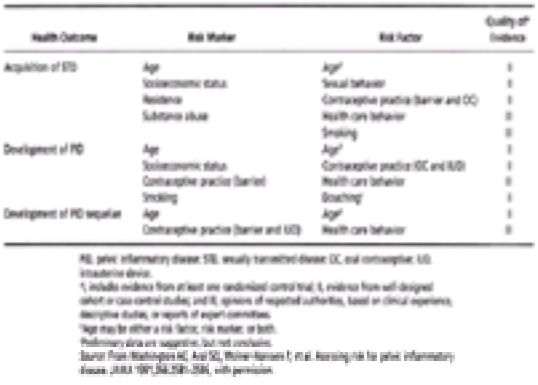
Initial studies assessing risk factors associated with PID focused on demographic and social indicators. More recently, the important roles of sexual behavior, contraceptive practice, health care behavior, and other individual behaviors and practices have been stressed (9,23,24 and 25) (Table 14.1). In addition, risk factors for the development of PID sequelae have been assessed (Table 14.1 and Table 14.2).



Risk Variable	Development of PID	Development of PID sequelae
Demographic and social indicators		
Age	↑	↓
Socioeconomic status	↑	NA
Marital status	↑	NA
Residence, rural or urban	↓	NA
Individual behavior and practices		
Sexual behavior		
No. of partners	NA	NA
Age at first coitus	NA	NA
Frequency of sexual intercourse	NA	NA
Rate of acquiring new partners	NA	NA
Contraceptive practice		
Barrier	↓	↓
Oral contraceptives	↓	NA
Intrauterine device	↑	↑
Health care behavior		
Evaluation of symptoms	↑	↑
Compliance with treatment	↑	↑
Sex partner referral	↑	↑
Others		
Douching	↑	NA
Smoking	↑	NA
Substance abuse	NA	NA
Menstrual cycle	↑	NA

↑, increased; ↓, decreased; NA, no association; PID, pelvic inflammatory disease.
Source: From Washington AE, Aral SO, Whitner-Hansen E, et al. Assessing risk for pelvic inflammatory disease and its sequelae. JAMA. 1991;266:2581–2586, with permission.

TABLE 14.1. RISK FACTORS OR RISK MARKERS FOR DEVELOPMENT OF PID AND PID SEQUELAE



Health Outcome	Risk Marker	Risk Factor	Quality of Evidence
Acquisition of STD	Age	Age[a]	II
	Socioeconomic status	Sexual behavior	II
	Residence	Contraceptive practice (barrier and OC)	II
	Substance abuse	Health care behavior	III
		Smoking	III
Development of PID	Age	Age[a]	II
	Socioeconomic status	Contraceptive practice (OC and IUD)	II
	Contraceptive practice (barrier)	Health care behavior	III
	Smoking	Douching[c]	II
Development of PID sequelae	Age	Age[a]	II
	Contraceptive practice (barrier and IUD)	Health care behavior	III

PID, pelvic inflammatory disease; STD, sexually transmitted disease; OC, oral contraceptive; IUD, intrauterine device.
[a], includes evidence from at least one randomized control trial; II, evidence from well-designed cohort or case-control studies; and III, opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
[a]Age may be either a risk factor, risk marker, or both.
[c]Preliminary data are suggestive, but not conclusive.
Source: From Washington AE, Aral SO, Whitner-Hansen E, et al. Assessing risk for pelvic inflammatory disease. JAMA. 1991;266:2581–2586, with permission.

TABLE 14.2. PROBABLE RISK CATEGORY AND SUMMARY OF QUALITY OF EVIDENCE SUPPORTING ASSOCIATION BETWEEN RISK FACTOR AND PID

Women who have had previous PID are more likely to have recurrent infections (2,26,27). Flesh et al. (28) demonstrated that patients with PID were 2.3 times more likely than control patients to have a history of previous PID. The exact mechanism for this increased susceptibility has not been delineated. Perhaps, as the result of acute salpingitis, the fallopian tube loses some of its natural protective mechanisms against microorganisms. Gregg et al. (29) demonstrated that the gonococcus

produces a lipopolysaccharide toxin that destroys fallopian tube cilia, and using scanning electron microscopy, Draper et al. (30) noted that there is loss of the normal fallopian tube endothelial architecture after acute salpingitis. Additional explanations include women with gonococcal or chlamydial PID are more likely to be reexposed to these putative agents and that certain organisms such as *C. trachomatis* may remain as latent infection in the fallopian tube after clinical response (31).

Demographic Factors

Demographic and social indicators of risk, which have been suggested as risk factors for PID, include age, socioeconomic status, marital status, and rural or urban residence (Table 14.1) (23). Age, an important risk marker for PID, is inversely related to PID rates (7,9). Thus, adolescent girls are at significant risk of developing acute salpingitis. Westrom (7) reported that nearly 70% of women with acute salpingitis were younger than 25 years, 33% experienced their first infection before the age of 19, and 75% were nulliparous. In Sweden, the risk of developing acute PID in the sexually active 15-year-old age-group was 1:8, with the risk falling to 1:10 for 16-year-olds and the risk decreasing to 1:80 in women 24 years or older (7,32). Similar results were reported by Bell and Holmes who noted that sexually active adolescent girls were three times more likely to be diagnosed with PID than 25- to 29-year-old women (33). It has been suggested that the adolescent population is at greater risk because this population has a high prevalence of STDs, has multiple sexual partners, and tends not to use contraceptives—many of which (i.e., birth control pills, diaphragms, and condoms) protect against the development of acute PID. In addition, the postpubertal adolescent is relatively estrogen dominant, with a resultant cervical ecotype that provides a greater target for attachment of *C. trachomatis* and *N. gonorrhoeae.* Although adolescents are at increased risk for PID, women in the 15- to 24-year age-group with PID have less PID-associated sequelae such as infertility than older women with PID (34,35).

Socioeconomic measures have been associated with increased risk for PID. These include (a) low levels of education (6,36,37); (b) unemployment (36); and (c) low income (38). Although these appear to be markers for PID risk, this association may well be an artifact of the relationship between socioeconomic status and the prevalence of STDs and sexual and health behaviors (23). Although residence in urban inner-city areas has been suggested as a risk marker for PID, no studies have been reported that compared PID rates among rural and urban populations. On the other hand, several studies have addressed the issue of marital status and noted that women in the “never married” category have higher rates of PID (37,39), as well as those in the “divorced” or “separated” category (10,40). Jossens et al. (41) demonstrated in a multivariate analysis of hospitalized women that the African-American race was associated with chlamydial and gonococcal PID (odds ratio [OR], 2.56; 95% CI, 1.68–3.90).

Sexually Transmitted Diseases

Gonorrhea, chlamydial infection, and bacterial vaginosis (BV) are the most important risk factors for PID (3). There is a strong correlation between exposure to STD organisms and PID. Swedish studies noted that up to 75% of acute PID in women younger than 25 years was associated with culture or serologic evidence of infection with *N. gonorrhoeae, C. trachomatis,* or *Mycoplasma hominis* (42). In the United

States, recent studies have confirmed this association, with recovery of *N. gonorrhoeae* or *C. trachomatis* in 50% to 80% of patients hospitalized with acute PID (42,43,44 and 45). In an analysis of risk factors associated with PID of differing microbial etiologies among 589 hospitalized patients with PID, we reported that an STD organism was present in 65% of PID cases, with *N. gonorrhoeae* and *C. trachomatis* recovered from 324 (55%) and 129 (22%) of the patients, respectively (41). Eschenbach et al. (5) reported that a history of prior uncomplicated cervical gonococcal infection was present among patients with acute PID compared with controls. Similarly, Wolner-Hanssen et al. (46) demonstrated that women with PID have increased rates of previous asymptomatic chlamydial cervicitis. It has been suggested that acquisition of a new gonococcal cervical infection might reactivate latent chlamydial infection of the fallopian tube (2,47).

Sexual Behavior

Although STD organisms are clearly involved in the etiology of STD-related PID, the role of sexual behavior in the development of PID remains poorly defined (23,48). In particular, studies have failed to differentiate between the role of sexual behavior as a risk factor for acquisition of STD-associated lower genital tract infection and the subsequent development of PID (9). However, several aspects of sexual behavior have been proposed to be associated with an increased risk of PID (Table 14.1). These include (a) multiple sex partners (36,37,39); (b) high frequency of sexual intercourse (36,37,39); (c) rate of acquisition of new sex partners within previous 30 days (36); and (d) age at first sexual intercourse (9). Both multiple lifetime partners (36,37,38 and 39) and multiple current partners (36,50) have been reported to be risk factors for PID. In a recent case-control study of PID risk factors, we identified more than one sex partner in the previous 30 days as a significant risk factor (OR, 11.08; 95% confidence interval [CI], 4.31–28.50), whereas lifetime number of partners was not associated with an increased risk for PID (49). The definition of multiple partners that we use is “more than one partner within a 30-day period.” Thus, the risk factor is not serially monogamous relationships, but rather multiple consorts over a brief time. It is important to recognize that it is not the presence of multiple partners per say that produces an increased risk for PID, but the fact that multiple partners increases the risk of being exposed to a PID-associated STD.

Coitus during menses has also been suggested as a risk factor for PID. In a case-control study comparing 135 women with PID to 740 controls from an STD clinic, Eschenbach et al. (51) noted that vaginal intercourse during the menses increased the risk for gonococcal and anaerobic and aerobic endogenous PID. Similarly, among hospitalized patients with acute PID analyzed in a case-control study, we reported that sexual intercourse with the last menses was a significant risk factor for PID (OR, 5.22; 95% CI, 1.88–14.48) (49).

Contraceptive Use

Use of different contraceptive methods has a major impact on the risk of acquiring STDs, PID, and sequelae of PID such as TFI or ectopic pregnancy (2,3,9,23,52). Previous investigations have demonstrated that nonusers of contraceptives are at increased risk for PID (36,37). Similarly, in a more recent case-control study, we demonstrated that lack of contraception was a significant risk factor for PID (OR, 7.60; 95% CI, 4.10–14.09) (49).

Barrier methods (mechanical and chemical) when properly used decrease the risk of STDs, PID, and sequelae of PID (2,3,9,23,52). Condoms when used appropriately are highly effective in decreasing the risk of acquisition and transmission of STD organisms associated with PID (e.g., *N. gonorrhoeae* and *C. trachomatis*) (53,54 and 55). In addition, condom use has been reported to decrease the risk of developing PID (54,55 and 56). Similarly, use of condoms has been associated with decreased risk of TFI (57) and ectopic pregnancy (58).

Diaphragm use has also been reported to decrease the risk for PID (56) and TFI (57). Whether the protective effect is due to the diaphragm alone is unclear. It has been suggested that vaginal spermicides decrease the risk of acquiring bacterial STDs, particularly *N. gonorrhoeae* and *C. trachomatis* (59,60), and consequently may also decrease the risk of PID.

The IUD is an additional predisposing factor (3,4 and 5,27,61,62,63,64,65,66 and 67). As noted by Washington et al. (23), most studies have found an increased risk of PID and its sequelae among IUD users, with the increase ranging from twofold to ninefold. The World Health Organization has reported that in the most objective studies comparing IUD use with no contraceptive use, the increase is in the range of 1.5 to 2.6 (68). As summarized by Westrom and Eschenbach (4), at least 20 controlled studies from the 1960s through the 1980s reported a twofold to fourfold increased risk of PID or sequelae of PID among users of IUDs compared with women using other or no contraceptives. Initially, no particular IUD was implicated as having a statistically significant increased risk more than the other brands. However, Kaufman et al. (61) reported that compared with nonusers, Dalkon Shield users had a 13-fold increased risk; Lippes loop and Saf-T-coil users had an eightfold increased risk, and Cooper 7 users had a fourfold increased risk in developing acute salpingitis. In addition, the overall risk for salpingitis doubled at 5 years of continuous use in the Kaufman et al. study. In a follow-up study, these authors reported that the age-adjusted relative risk for PID with the use of an IUD within 1 month of admission was 8.6 (CI, 5.3–13.8) (67). The risk was highest for the Dalkon Shield but was significantly increased for Lippes loop (relative risk, 13.3), Saf-T-coil (relative risk, 24.1), and copper-containing devices (relative risk, 6.8). However, they no longer demonstrated that the risk was associated with duration of use. Lee et al. (66) subsequently demonstrated that women wearing Dalkon Shield IUDs were at statistically significant increased risk of developing acute PID. Compared with the risk in women using no contraception, the relative risk of PID in women using the Dalkon Shield was 8.3. This represented a fivefold increase in risk compared with women using other types of IUDs. Moreover, the risk to Dalkon Shield wearers continued to progressively increase in proportion to duration of use. This phenomenon was not seen with other IUDs, whose risk peaked 4 months after insertion. However, copper devices were not included in the long-term user group. During the first 4 months after insertion, copper-containing IUDs were associated with the highest risk for PID (66). As reported by Fairley (69), women using IUDs have an increased risk of PID in the first 1 to 3 months after insertion. Most likely, this is related to the introduction of microorganisms into the uterus with insertion. Although the rate of PID decreases after the initial postinsertion period, it remains higher than that of nonusers of IUDs, as demonstrated in case-control studies of acute PID (3,64), tubal infertility (70,71 and 72), and ectopic pregnancy (73). Animal model investigations have suggested that multifilament strings are a major contributing factor to the increased risk for PID (74,75 and 76). Although all IUD

strings facilitate access to the upper genital tract for bacteria from the vagina and cervix, multifilament-type strings have an increased ability to do this. The second factor is the ability of the shield itself to interfere with the normal intrauterine host defense mechanisms. Because of its large contact area with the endometrial surface, the shield is more likely to alter these defenses, cause endometrial abrasion and ulceration, and initiate what Burnhill (77) has termed “the syndrome of progressive endometritis,” which leads to acute PID. Recently, results from the PID Evaluation and Clinical Health (PEACH) study (78) (multiinstitutional treatment trial of PID), comparing contraceptive use in 290 women with histologic endometritis with 253 women without it, demonstrated that IUD users had a marked increased risk of PID, with an OR of 13.1 (95% CI, 1.6–109.3).

In contrast, most studies have shown that oral contraceptives (birth control pills) reduce the risk for symptomatic, clinically apparent acute PID by 40% to 60% (63,64,66,79,80 and 81). The mechanism for such protection remains speculative. Perhaps the effect of birth control pills on cervical mucus precludes the ascension of vaginal and cervical microorganisms into the upper genital tract. An additional explanation is that birth control pills cause modifications of the immune response (36,57). Women using birth control pills have a shorter duration of menses and less flow; this could result in a shorter “window” for microorganisms to gain access to the uterus or fallopian tubes. In addition, birth control pills result in atrophy of the endometrium and decrease the uterine contractility, which assists the movement of bacteria from the vaginal cervix into the upper genital tract (22). Svensson et al. (79) and others (80,81) reported that, in addition to protecting against PID, the use of birth control pills both ameliorated PID if it occurred and was associated with a better prognosis for future fertility than was seen in women with acute PID using other contraceptive methods or none. Although Washington et al. (82) raised the concern of whether birth control pills protected against chlamydial PID, Wolner-Hanssen et al. (81) recently reported a reduction in the risk for chlamydial PID similar to that seen with gonococcal and nongonococcal, nonchlamydial PID. Cramer et al. (57) demonstrated that there was a significant increase or decrease in the risk of tubal infertility among women using oral contraceptives.

Health Care Behavior

Health care–seeking behavior influences the risk of PID (9). Washington et al. (23) reported that early detection and effective treatment of STD and PID in women and their sex partners will decrease the risk of PID and its sequelae. Hillis et al. (83) demonstrated that delayed treatment of PID had a significant adverse effect on fertility. When treatment was delayed for 3 or more days, the rate of impaired fertility was 19.7%, compared with 8.3% when treatment commenced within 2 days of the onset of symptoms (adjusted OR, 2.8; 95% CI, 1.3–6.1). Thus, prompt evaluation, compliance with management instructions, and treatment of sex partners probably decrease the risk of PID and its sequelae (9).

Douching

Vaginal douching has recently been the focus of considerable interest and controversy as a potential risk factor for PID (23,84,85) and PID-associated sequelae (23,86,87). Since the initial brief reports by Hirst (88) and Neuman and DeCherney (89), suggesting that vaginal douching was associated with PID, several studies have demonstrated that women with acute PID are more likely to have a history of

douching than women who do not douche (49,85,86,90,91). In a case-control study that included multivariate analysis to adjust for cofounders, Wolner-Hanssen et al. (85) reported that douching during the previous 2 months was associated with an adjusted relative risk of 1.7 (95% CI, 1.04–2.82) for laparoscopically confirmed or endometrial biopsy–confirmed PID. This risk was significantly related to frequency of douching; women who douched three or more times per month were 3.6 times more likely to have PID than those who douched once per month. When analyzed by race, douching remained significantly associated with PID only among non-black women (85). These authors attributed the lack of significance among black women to the high prevalence of douching in the control group of black women. Using the 1988 National Survey of Family Growth, cycle IV, Aral et al. (38) reported that douching was independently related to PID even after adjusting for age, marital status, lifetime partners, STD history, and age at first intercourse. Similar to the findings of Wolner-Hanssen et al. (85), this relationship was found only in white women, as the high prevalence of douching in black women precluded demonstrating significance of douching among black women (38). In an uncontrolled study, Forrest et al. (84) noted that 76% of hospitalized cases of PID reported a history of douching. Among women with multiple episodes of PID, 89% reported douching, compared with 71% of women having their initial episode of PID (84). In a case-control study of 234 PID cases and 122 matched controls, Joessens et al. (49) reported a twofold increased risk for PID associated with douching (OR, 2.20; 95% CI, 1.14–4.23). However, the sample size was inadequate to assess this relationship with racial groups, and in a multilogistic regression analysis, the significance did not remain. Once again, a very high prevalence of douching among black women was noted (49). Recently, in a population-based case-control study, Scholes et al. (91) reported that women who had douched in the previous 3 months had a risk for PID of 2.1 (95% CI, 1.2–3.9), compared with women who never douched, after controlling for other risk factors. These authors also noted that women who douched more frequently were at increased risk.

Several case-control studies have demonstrated that vaginal douching is associated with ectopic pregnancy, a major sequela of acute PID (86,87,92). In a case-control study with 155 ectopic pregnancies and 465 controls, Chow et al. (86) reported that douching was associated with a twofold increase in ectopic pregnancy (OR, 2.0; 95% CI, 1.03–4.0). When only commercial douching preparations were used, there was a fourfold increased relative risk for ectopic pregnancy (OR, 4.0; 95% CI, 1.6–12.7). In a concurrent case-control study in which 306 ectopic pregnancies were matched with 266 pregnant controls, Chow et al. (87) noted that douching had a twofold increase in risk of ectopic pregnancy (relative risk, 2.2; 95% CI, 1.4–3.7). In this study, the population attributable risk was 0.45, which was only exceeded by previous chlamydial infection. Daling et al. (92) reported results from a case-control study that demonstrated an elevated risk for ectopic pregnancy was associated with douching in women with more than one lifetime sexual partner (OR, 1.6; 95% CI, 1.1–2.3) and women who had serologic evidence of prior chlamydial infection (OR, 2.4; 95% CI, 0.8–7.3). On the other hand, Phillips et al. (93) failed to confirm that douching was associated with ruptured ectopic pregnancies. In this study, only current cigarette smoking was associated with an increased risk for ectopic pregnancy.

Although these studies have suggested an association between douching and PID and sequelae of PID, they do not prove causality. In favor of such a relationship is the consistency of the findings (with the exception of the study by Phillips et al. [93]), the dose-response relationship seen with frequency of douching, the use of multivariate analysis controlling for confounding variables, and the biologic

plausibility. As to the latter, douching could result in pushing or flushing microorganisms from the vagina and cervix into the upper genital, thus increasing the risk for upper genital tract infection (23). Alternatively, douching may alter the vaginal microbial ecosystem, resulting in colonization with organisms such as *N. gonorrhoeae* and *C. trachomatis,* or predispose for the development of BV with subsequent increased risk for PID. Clearly, further large-scale studies that focus on douching behavior are required to settle this issue. These studies must address douching technique, timing to sexual activity, relationship to menses, risk factors for STDs and PID, and contraceptive use. Such studies ideally should be prospective.

Additional Risk Factors

Additional factors that have been implicated as risk factors for PID include cigarette smoking (37,94), substance abuse (36,95), and menses (99). In studies by Marchbanks et al. (37) and Scholes et al. (94), women who were current cigarette smokers had a twofold increased risk of PID. Although Scholes et al. (94) demonstrated a dose-response relationship between increased quantity of cigarettes smoke and PID, the study by Marchbanks et al. (37) failed to do so.

A relationship between the symptomatic onset of acute PID and the menstrual period has long been assumed clinically (23). Sweet et al. (96) reported that women with chlamydial or gonococcal PID are significantly more likely to develop symptoms within 7 days of the onset of menses. The reverse was true for PID with nongonococcal, nonchlamydial bacteria. Wolner-Hanssen et al. (36) and Fullilove et al. (95) have reported that alcohol and illicit drug use, particularly cocaine, are associated with PID.

ETIOLOGY

PID is caused by the ascension of microorganisms from the lower genital tract (cervix and vagina) into the upper genital tract. Thus, the etiology of PID is polymicrobic in nature and various microorganisms have been recovered from the upper genital tract of women with acute PID (1,3,9,41,42,43 and 44,97,98,99,100,101,102,103 and 104). Among these organisms are *N. gonorrhoeae, C. trachomatis,* genital mycoplasmas, anaerobic and aerobic bacteria from the endogenous vaginal flora such as *Prevotella* sp (formerly *Bacteroides* sp), *Peptostreptococci* sp, *Gardnerella vaginalis, Escherichia coli, Haemophilus influenzae,* and aerobic streptococci. As noted by Rice and Schachter (105), most proven cases of PID are associated with *N. gonorrhoeae* or *C. trachomatis.* Jossens et al. (41) confirmed this finding in a large series (n = 589) of hospitalized cases of acute PID in which an STD organism was present in 65% of cases—*N. gonorrhoeae* or *C. trachomatis* was recovered from 324 (55%) and 129 (22%), respectively (Fig. 14.2). In 30% of cases, only anaerobic and facultative bacteria were isolated; in addition, anaerobic and facultative organisms were frequently (nearly 50%) recovered from the upper genital tract of patients with an STD organism (41). Similarly, Rice and Schachter (105) noted that 25% to 50% of PID cases do not have detectable chlamydial or gonococcal infection, but other anaerobic and facultative bacteria have been isolated from the upper genital tract. Many of these non-STD organisms are similar to those associated with BV (106,107).

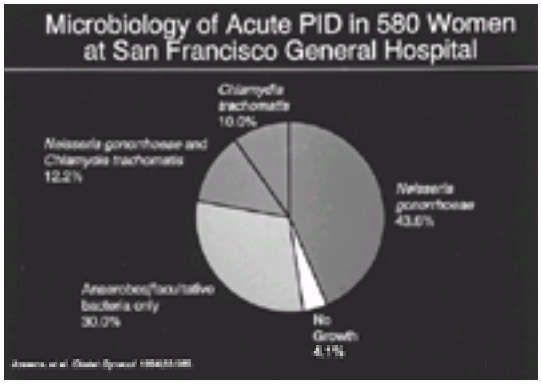


FIGURE 14.2. Microbiologic etiology of acute pelvic inflammatory disease in hospitalized women.

Multiple studies have clearly established that the microbial etiology of acute PID is most appropriately determined by specimens obtained directly from the upper genital tract (3,98,102). Microorganisms recovered from patients with acute PID are divided into two broad groups: sexually transmitted organisms and endogenous organisms (3,108).

N. gonorrhoeae and *C. trachomatis* are the major sexually transmitted organisms that cause acute PID. On the other hand, the etiologic role of genital mycoplasmas is unclear, and although HSV, CMV, and *Trichomonas vaginalis* have been isolated from the pelvis of women with acute PID, their ability to cause PID has not been established (3,109).

Attention is currently focused on “unrecognized” (formally known as “silent” or “atypical”) PID, a term used to characterize the situation in which women with documented TFI have no history of being diagnosed or treated for PID despite chronic inflammatory residua being confirmed (21). Unrecognized PID presents with a typical clinical picture (e.g., abdominal/pelvic pain, abnormal uterine bleeding, and mucopurulent endocervical discharge) (109,110). Whether the microorganisms that are the putative agents for clinically apparent PID are associated with unrecognized PID remains to be confirmed. Preliminary studies suggest that both the STD organisms, *N. gonorrhoeae* and *C. trachomatis,* and the BV-associated microorganisms are also associated with unrecognized PID (4) (H. Wiesenfeld and R. L. Sweet, *unpublished data*).

Neisseria gonorrhoeae

In the United States, nontuberculous acute PID was traditionally separated into gonococcal and nongonococcal disease. This division was based solely on the recovery of *N. gonorrhoeae* from the endocervix of patients with acute PID. Studies using endocervical cultures implicated the gonococcus as the causative agent in 33% to 81% of the cases of acute PID (6,27,97,111,112,113,114,115,116,117,118 and 119). More recent studies in which specimens were obtained from the abdominal cavity or fallopian tubes demonstrate recovery of *N. gonorrhoeae* from the endocervix in 39% and from the abdominal cavity/fallopian tubes in 18% of total

patients and 43% of patients with *N. gonorrhoeae* isolated from the cervix (Table 14.3). Generally, in populations with high endemic rates of gonorrhea, a high proportion of acute PID is associated with *N. gonorrhoeae* (4). Thus, in many areas of the United States, *N. gonorrhoeae* has been recovered in 40% to 50% of acute PID cases (4). As demonstrated by Westrom (130), in areas where the incidence of gonorrhea decreased, the proportion of PID cases associated with *N. gonorrhoeae* has also decreased. Thus, in Sweden without endemic gonorrhea, *N. gonorrhoeae* is recovered in less than 5% of acute PID cases (130).

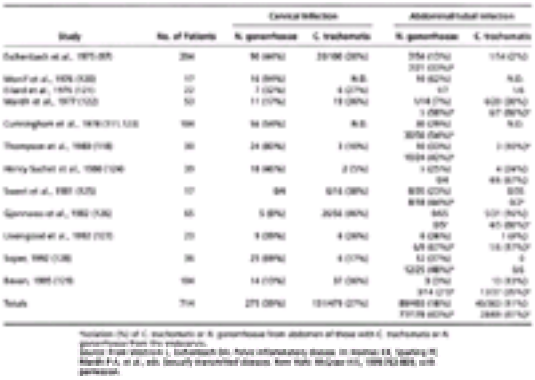


TABLE 14.3. ISOLATION OF *NEISSERIA GONORRHOEAE* AND *CHLAMYDIA TRACHOMATIS* FROM THE ENDOCERVIX AND ABDOMINAL CAVITY/FALLOPIAN TUBES IN WOMEN WITH ACUTE PELVIC INFLAMMATORY DISEASE

Recently, the PEACH study (the largest prospective cohort of acute PID in the United States) reported that among 274 patients with acute PID confirmed by histologic endometritis, *N. gonorrhoeae* was isolated in only 11 (4%), with a range of 3% to 13% among four sites (Pittsburgh, Birmingham, Charleston, and Providence) (131).

Chlamydia trachomatis

C. trachomatis has received considerable attention and is now firmly established as a major etiologic agent in acute PID. In Chapter 5 (Chlamydial Infections), the role of *C. trachomatis* in the etiology of PID is presented in detail. It is briefly reviewed in this section.

Studies in the Scandinavian countries were the first to demonstrate the important role of *C. trachomatis* in the etiology of acute PID (121,122,126,133,134,135,136,137,138 and 139) (Table 14.4). These studies reported the recovery of *C. trachomatis* from the cervix in 22% to 47% of women with acute PID. Of more significance, *C. trachomatis* was recovered from the fallopian tubes in 9% to 30% of women with visually confirmed acute PID (121,122,127). Scandinavian studies, using serologic surveillance, suggested that *C. trachomatis* is associated with 23% to 62% of acute PID cases (121,127,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148

and 149).

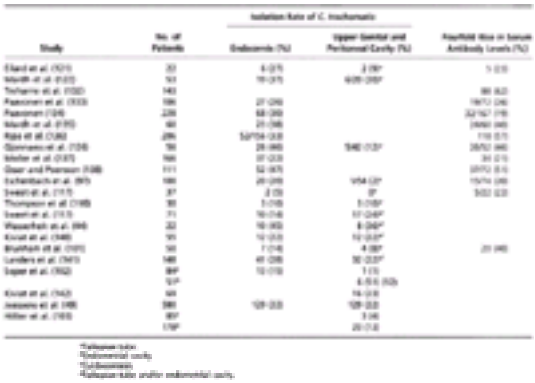


TABLE 14.4. *CHLAMYDIA TRACHOMATIS* IN ACUTE PELVIC INFLAMMATORY DISEASE

Initial investigations in the United States failed to confirm that chlamydia was a major putative agent in acute PID. Eschenbach et al. (97) recovered *C. trachomatis* from the peritoneal cavity in only 1 of 54 cases, despite a 20% isolation rate of this organism from the cervix. In the first laparoscopy study performed in the United States, Sweet et al. (43,117) failed to recover *C. trachomatis* from the fallopian tube exudate in 37 patients. Wasserheit et al. (44) and Thompson et al. (118) showed that 10% of women with acute PID had chlamydiae isolated from the culdocentesis aspirates. However, serologic data obtained from studies in the United States showed a fourfold rise in chlamydial antibodies in approximately 20% of acute cases (97,117). The conflicting findings from Scandinavia and the United States were felt to be due to several factors. First, in Sweden, specimens for chlamydial cultures were obtained using biopsy or needle aspiration of the fallopian tube; in the United States, studies had used cultures from peritoneal fluid or tubal exudate. *C. trachomatis* is an intracellular organism, so fresh infected cells, such as those obtained by way of biopsy, may be necessary to recover the organism. Second, the patient population studied may be different; the Swedish investigators studied women with a milder disease than was usually admitted to hospitals and studied in the United States. In fact, it has been suggested by Svensson et al. (143) that patients with milder PID are more likely to have *C. trachomatis* as the causative agent. These investigators noted that the women with *C. trachomatis* as the causative agent were more likely to be afebrile and have longer-standing disease of milder type than women with gonococcal or nongonococcal, nonchlamydial disease. Paradoxically, though, at laparoscopy, those women with *C. trachomatis* infection based on serologic data had the most severe fallopian tube involvement and the highest estimated erythrocyte sedimentation rates (ESRs) (143). This Scandinavian group of investigators has noted that patients with anaerobes recovered were more likely to be febrile, appeared to have more severe clinical symptoms and signs, and were prone to have associated inflammatory adnexal masses (L. Westrom, *personal communication,* 1982).

Most recent studies have demonstrated a definite role for *C. trachomatis* as an

etiologic agent for acute PID in the United States. Using specimens obtained from the upper genital tract (endometrial cavity or fallopian tubes), Sweet et al. (43) provided direct evidence for the etiologic role of *C. trachomatis* in hospitalized women with acute PID. These investigators recovered *C. trachomatis* from 17 (24%) of 71 of these patients. Confirmation of a major role for *C. trachomatis* in the etiology of acute PID in the United States has been provided by Wasserheit et al. (44), who reported that 14 (61%) of 23 women with salpingitis or plasma cell endometritis had *C. trachomatis* identified in the upper genital tract. Similarly, Kiviat et al. (140) and Landers et al. (141) recovered *C. trachomatis* from the upper genital tract in 22% and 22% of PID patients, respectively. In a study of 580 hospitalized patients with acute PID, Joessens et al. (49) recovered *C. trachomatis* from the upper genital tract in 129 (22%) patients. Hillier et al. (103) reported isolation of *C. trachomatis* from the endometrium in 23 (13%) of 178 patients with histologic endometritis and clinical acute PID. A summary of the results from laparoscopy studies, in Table 14.3, demonstrates recovery of *C. trachomatis* from the fallopian tubes/abdominal cavity in 40 (10%) of 363 patients with confirmed acute PID. In these studies, *C. trachomatis* was isolated from the fallopian tubes/abdominal cavity in 28 (41%) of 69 patients with PID with chlamydial cervical infection. Generally, European studies from the 1970s and 1980s reported isolation rates of *C. trachomatis* ranging from 25% to 50% in acute PID, whereas those from the United States showed lower rates of chlamydial infection (4). Thus, clinicians must appreciate that current evidence strongly supports a putative role for *C. trachomatis* in acute salpingitis. This has major implications for clinical management, as is discussed in a subsequent section.

Additional epidemiologic data further suggest that chlamydia plays a role in infertility due to tubal obstruction and salpingitis (124,144,145,146,147,148,149,150,151,152 and 153). These studies have demonstrated in various populations and geographic areas that women with TFI are significantly more likely to have had previous systemic chlamydial infection as documented serologically than pregnant controls or patients without TFI. A similar association between previous chlamydial infection and ectopic pregnancy has been recently demonstrated (87,147,154,155 and 156) (Chapter 5, Chlamydial Infections, Table 5.7). Thus, the two major sequelae of acute PID—tubal infertility and ectopic pregnancy—have been associated with prior chlamydial infection. In Chapter 5 (Chlamydial Infections), a detailed assessment of the association between chlamydial infection and tubal infertility and ectopic pregnancy can be found. These epidemiologic studies also led to the concept of unrecognized PID because about one half of women with TFI and serologic evidence of previous chlamydial infection had no history of being diagnosed or treated for acute PID (124,144,145,146,147,148,149,150,151,152 and 153). Although very suggestive of a direct etiologic role in tubal infertility for *C. trachomatis,* these seroepidemiologic studies do not prove causation. However, recent investigations have provided a model for the pathogenesis of chlamydial salpingitis and its sequelae, which is discussed in depth later (see the section on pathogenesis) (157,158,159,160,161,162 and 163). Briefly, it is hypothesized that chlamydial PID is an immune-mediated disease resulting from immune responses to a chlamydial heat shock protein 60 (Hsp 60) (157,158,159,160,161,162 and 163). Thus, *C. trachomatis* elicits an inflammatory response similar to a delayed hypersensitivity reaction with resultant damage to the fallopian tube (157,158,159,160,161,162 and 163). This hypersensitivity response is similar to the pathogenic mechanism by which *C. trachomatis* produces scarring and blindness in ocular trachoma (164).

Further evidence that supports the role of *C. trachomatis* in acute PID has been shown in animal model work, which has demonstrated the ability of chlamydia to

produce acute salpingitis (165,166,167,168,169,170,171 and 172). These have included use of the guinea pig inclusion conjunctivitis agent in the guinea pig, the mouse pneumonia biovar of *C. trachomatis* in the mouse, and human *C. trachomatis* in the Grivet monkey (165,166,167,168,169,170,171 and 172).

Genital Tract Mycoplasmas

The genital tract mycoplasmas, *Mycoplasma hominis, Ureaplasma urealyticum,* and *Mycoplasma genitalium* have been suggested as potential pathogens in the etiology of acute salpingitis (173,174,175 and 176). However, their role remains controversial. Although *M. hominis* and *U. urealyticum* have been frequently recovered from the lower genital tract of women with PID, no difference exists between the rates of isolation from the cervices of these patients and sexually active control patients (97,173). Moreover, the genital tract mycoplasmas have been recovered infrequently (2% to 20%) from the peritoneal cavity or fallopian tubes of patients with salpingitis (Table 14.5) (97,117,174). Speculation as to a role of genital mycoplasmas in the etiology of PID has focused predominantly on *M. hominis.* For *M. hominis,* Mardh and Westrom (174) reported a cervical isolation rate of 52%; Eschenbach et al. (97) recovered *M. hominis* from lower genital tracts of 145 (72%) of 204 women with acute PID, and Møller et al. (175) recovered it from 91 (55%) of 166 PID cases. Serologic studies have also suggested a role for *M. hominis* in the etiology of acute PID (97,173,174,175 and 176). In these studies, antibodies to *M. hominis* were present in one fourth to one half of women with acute PID. However, *M. hominis* is infrequently recovered from the fallopian tubes of women with acute PID (Table 14.5). In addition to the low recovery rate from the fallopian tube, *in vitro* studies with fallopian tube explant systems have suggested that mycoplasmas may be commensals rather than pathogens in acute PID. Taylor-Robinson and Carney (177) reported that despite proliferation of *M. hominis,* no apparent tubal damage was produced. This is in contradistinction to the circumstance when *N. gonorrhoeae* or *Bacteroides fragilis* are placed in a similar system and extensive epithelial damage occurs and the tubal epithelium is completely destroyed (178,179). However, the *in vitro* fallopian tube explant system precludes the immune response and host defense mechanisms, which may be important in the pathogenesis of acute salpingitis (180). Using the Grivet monkey model, Møller et al. (181) reported that *M. hominis* produces a parametritis rather than an acute salpingitis, and this could possibly explain the failure to recover mycoplasmas except in a few cases from the fallopian tubes. Using scanning electron microscopy, Mardh et al. (182) showed that *M. hominis* induced pathologic swelling in fallopian tube cilia in organ culture systems. Although results obtained with serologic studies and cervical isolation approaches are suggestive, the role of *M. hominis* in the etiology of acute PID remains unclear. Perhaps *M. hominis* participates in acute PID as the result of its association with BV.

Study	Cervical Isolation (%)	Tubal Isolation (%)	Antibody Titer Change (%)
Mycoplasma hominis			
Sweet et al., 1979 (117)	73	6	
Eschenbach et al., 1975 (97)	72	4	20
Mardh and Westrom, 1970 (110)	62	8	
Thompson et al., 1980 (118)	60	17	
Møller, 1983 (175)	55		30
Mardh et al., 1981 (176)			40
Bevan, 1995 (129)	38	0	
Ureaplasma urealyticum			
Eschenbach et al., 1975 (97)	81	2	10
Mardh and Westrom, 1970 (110)	56	4	
Sweet et al., 1979 (117)	54	15	
Thompson et al., 1980 (118)	33	20	
Henry-Suchet et al., 1983 (21)	24	17	
Sweet et al., 1981 (125)		9	

Source: From Westrom L, Eschenbach DA. Pelvic inflammatory disease. In: Holmes KK, Sparling PF, Mardh P-A, et al., eds. Sexually transmitted diseases. New York: McGraw-Hill 1999:783–801, with permission.

TABLE 14.5. EVIDENCE OF GENITAL MYCOPLASMA INFECTION AMONG WOMEN WITH ACUTE PELVIC INFLAMMATORY DISEASE

Although *U. urealyticum* has been frequently recovered from the cervix of women with acute salpingitis (range, 24% to 81%), isolation rates from the fallopian tube are much lower (Table 14.5). Eschenbach et al. (97) also demonstrated a significant increase in antibody to *U. urealyticum* in 20% of women with acute PID. However, Møller et al. (183) were unsuccessful in their attempt to produce salpingitis in a monkey model with *U. urealyticum.* In general, the consensus opinion is that if there is any role in the etiology of acute PID for *U. urealyticum,* it is minimal (3,4).

More recently, attention has focused on a third genital tract mycoplasma, *M. genitalium.* Although *M. genitalium* has been demonstrated in the cervix using polymerase chain reaction (PCR) amplification technology (184) and has produced salpingeal infections in animal models including nonhuman primates (185,186), no studies have been reported that demonstrate the presence of *M. genitalium* in tubal specimens from women with acute PID. Thus, its role in acute PID remains undetermined (4).

Other Sexually Transmitted Pathogens

The etiologic role of viruses in acute PID has not been extensively studied. In particular, a potential role has been suggested for the viral agents HSV-2 and CMV. Laparoscopy studies in the United States by Sweet et al. (117) and Wasserheit et al. (44) failed to demonstrate the presence of HSV in the cervices or fallopian tubes of patients with acute PID. Investigators in Finland reported the recovery of HSV from the cervix and the upper genital tract of a few women with laparoscopically confirmed acute PID (187,188). Wasserheit et al. (44) noted that CMV was recovered from the cervices in 6 (28%) of 22 women with acute PID. Moreover, they reported that CMV was associated with chlamydial cervicitis and postulated that chlamydial infection might reactivate latent CMV. *T. vaginalis* has been rarely recovered from the pelvis in women with acute PID (4). Although interesting, these findings require confirmation and the role of viral agents and protozoa in acute PID awaits further investigation.

Anaerobic And Facultative Bacteria

In the 1970s, it became apparent that the presence of pathogenic microorganisms in the endocervix was not absolute proof that such microorganisms are causally associated with upper genital tract infections such as salpingitis. Investigations using transvaginal culdocentesis and laparoscopy to obtain culture specimens from the peritoneal fluid or fallopian tube exudate demonstrated a poor correlation between the cervical and intraabdominal cultures. Despite isolation from the endocervix of patients with acute salpingitis, *N. gonorrhoeae* was recovered from only 6% to 70% of the peritoneal or tubal cultures (97,98,111,116,117 and 118,120,123,125,189). Investigations in the late 1970s using culdocentesis and appropriate anaerobic culture techniques resulted in the isolation of various aerobic and anaerobic bacteria from the peritoneal fluid of patients with acute PID (97,98,111,116,117 and 118,120,123,189). The most frequent organisms recovered in these studies were *N. gonorrhoeae* and anaerobic bacteria, including *Peptostreptococcus* and *Bacteroides* and *Prevotella* sp. A characteristic pattern evolved from these studies (Table 14.6). Although there was a high prevalence of *N. gonorrhoeae* in the cervix of these patients, less than one fourth of the cases had *N. gonorrhoeae* as the only organism recovered from an intraabdominal site. An additional one fourth of the patients had a mixture of *N. gonorrhoeae* plus mixed anaerobic-aerobic bacteria (predominantly anaerobes). The final 50% of the patients did not have *N. gonorrhoeae,* but only a mixture of anaerobic-aerobic bacteria were recovered from the abdominal cavity. These culdocentesis studies demonstrated that the etiology of acute PID is polymicrobic in nature and brought into question the exact role of *N. gonorrhoeae* in the pathogenesis of acute PID. Although several investigators (120,123,189) postulated that the gonococcus initiates acute PID and produces tissue damage and changes in the local environment, which in turn allows access to the upper genital tract for anaerobic and aerobic organisms from the vaginal and cervical flora, others (27,98,190) have suggested that not all PID follows gonococcal infection and that acute PID initially has a polymicrobial etiology. At the other extreme, Soper et al. (102) have suggested that BV, an overgrowth of anaerobic and aerobic flora of the vagina, may predispose or facilitate the ascension of *N. gonorrhoeae* into the upper genital tract.

		Culdocentesis		
Study	No. of Patients	Endocervical N. gonorrhoeae (%)	N. gonorrhoeae Only (%)	N. gonorrhoeae Plus Anaerobes and Aerobes (%)
Cunningham et al. (111)	104	56 (54)	12 (22)	18 (32)
Thompson et al. (118)	30	24 (80)	5 (21)	5 (21)
Eschenbach et al. (97)	54	21 (39)	6 (28)	1 (5)
Monif et al. (120)	17	16 (94)	5 (31)	5 (31)
Sweet et al. (98)	26	13 (50)	4 (31)	4 (31)
Chow et al. (189)	20	13 (65)		1 (5)
Total	251	143 (57)	32 (22)	34 (24)

TABLE 14.6. ISOLATION OF *NEISSERIA GONORRHOEAE,* ANAEROBES, AND AEROBES FROM CULDOCENTESIS ASPIRATES IN ACUTE PELVIC INFLAMMATORY DISEASE

However, there was concern that microorganisms obtained from cul-de-sac fluid, aspirated transvaginally, did not represent the microorganisms present in the fallopian tube. Sweet et al. (117) demonstrated a discrepancy between culdocentesis and fallopian tube isolates from women with acute PID. Culdocentesis specimens yielded greater numbers of bacteria common to the vaginal flora than the fallopian tube isolates. A subsequent study included ten patients using cultures from the fallopian tube, the cul-de-sac contained via laparoscopy, and the cul-de-sac obtained via transvaginal culdocentesis (98). Although close agreement between fallopian tube exudate and the cul-de-sac aspirate via laparoscopy was found, there was a poor correlation with the culdocentesis results, suggesting that contamination may occur during transvaginal culdocentesis. Soper et al. (191) confirmed the finding that the use of culdocentesis to obtain a microbiologic specimen from the peritoneal cavity is fraught with the problem of contamination by the vaginal flora.

The optimum microbiologic information for elucidating the etiology of acute PID would be obtained using specimens obtained directly from the site of infection—the fallopian tubes or the endometrial cavity. In 1980, Sweet et al. (98,117) reported their results from the first laparoscopy study of PID performed in the United States, with cultures obtained directly from the fallopian tube. These results are presented in Table 14.7. Although nearly 50% of the patients had *N. gonorrhoeae* recovered from the endocervix, the gonococcus was isolated from the fallopian tube in only 8 of 35 patients (23%). Of the patients with salpingitis with endocervical *N. gonorrhoeae,* only 24% had the gonococcus recovered from the fallopian tube. Anaerobic bacteria were the most frequent fallopian tube isolates from these women with acute salpingitis. In this initial work, *U. urealyticum* was rarely recovered from the fallopian tube, whereas no isolates of *M. hominis* or *C. trachomatis* were obtained. Subsequently, we have described the microbiologic results of cultures obtained from the upper genital tract (endometrial aspirates or fallopian tube specimens) of an additional 580 hospitalized women with acute PID (Table 14.8) (49). *N. gonorrhoeae* and *C. trachomatis* were recovered from 45% and 18%, respectively. However, nongonococcal, nonchlamydial bacteria were the most frequently recovered organisms and were present in 70% of cases. Again, anaerobic bacteria were the predominant isolates. The nongonococcal, nonchlamydial organisms identified are noted in Table 14.9. The most common included *Prevotella* sp (formerly *Bacteroides* sp), *Prevotella bivia* (*Bacteroides bivius*), *Prevotella disiens* (formerly *Bacteroides disiens*), *Peptostreptococcus* sp, *G. vaginalis,* group B streptococcus, and *E. coli.* Most recently, our group demonstrated that in nearly one third of hospitalized cases of acute PID, anaerobic and aerobic bacteria were the only organisms recovered from the upper genital tract (Fig. 14.2), and that among the two thirds of patients with *N. gonorrhoeae* or *C. trachomatis* isolated, 50% also had anaerobes and aerobes recovered (41). Thus, anaerobes and aerobes were associated with two thirds of the cases of acute PID (41).

Microorganisms	Fallopian Tube (N = 35) No. (%)	Culdocentesis (N = 35) No. (%)
N. gonorrhoeae	8 (23)	11 (31)
N. gonorrhoeae only	6 (17)	3 (8.5)
N. gonorrhoeae in combination with other bacteria	2 (6)	8 (23)
Aerobic bacteria only	1 (3)	1 (3)
Anaerobic bacteria	10 (29)	20 (57)
Anaerobes only	3 (8.5)	5 (14)
Mixed anaerobes-aerobes	7 (20)	15 (43)
Mycoplasma hominis	0	1 (3)
Ureaplasma urealyticum	3 (8.5)	6 (17)
Chlamydia trachomatis	0	0
No growth	13 (37)	9 (26)

Source: From Sweet RL, Draper DL, Schachter J, et al. Microbiology and pathogenesis of acute salpingitis as determined by laparoscopy: what is the appropriate site to sample? *Am J Obstet Gynecol* 1980;138:985, with permission.

TABLE 14.7. DISTRIBUTION OF MICROORGANISMS ISOLATED FROM WOMEN WITH ACUTE PELVIC INFLAMMATORY DISEASE AT SAN FRANCISCO GENERAL HOSPITAL

Organism	No. of Patients Positive/No. of Patients Cultured	% Positive
Neisseria gonorrhoeae	172/380	45%
Chlamydia trachomatis	68/380	18%
Mycoplasma hominis	34/87	39%
Ureaplasma urealyticum	13/87	15%
Nongonococcal Nonchlamydial Bacteria	267/380[a,b]	70%

[a]Based on references 3, 43, 45, and 141.
[b]Primary plate isolates.

TABLE 14.8. MICROBIOLOGIC RESULTS FROM HOSPITALIZED PATIENTS WITH ACUTE PELVIC INFLAMMATORY DISEASE AT SAN FRANCISCO GENERAL HOSPITAL[a]

Prevotella [formerly Bacteroides] sp.	88	Gardnerella vaginalis	121
Prevotella bivia	72	Escherichia coli	25
Prevotella disiens	25	Nonhemolytic streptococci	49
Other Prevotella [Bacteroides] organisms	99	Group B streptococci	29
Peptostreptococcus asaccharolyticus	93	α-Hemolytic streptococci	45
Peptostreptococcus anaerobius	71	Coagulase-negative staphylococci	72

TABLE 14.9. NONGONOCOCCAL NONCHLAMYDIAL BACTERIA RECOVERED FROM THE UPPER GENITAL TRACT OF PATIENTS WITH ACUTE SALPINGITIS

AT SAN FRANCISCO GENERAL HOSPITAL (N = 188)

The frequent recovery of anaerobic and facultative (aerobic) bacteria from the upper genital tract of women with acute PID has been confirmed by other studies in Scandinavia and the United States (Table 14.10). Heinonnen et al. (100) reported that although *C. trachomatis* was the most common individual organism recovered from the fallopian tubes and endometria of patients with acute PID, nongonococcal, nonchlamydial bacteria were the most commonly recovered group of microorganisms (Table 14.10). Similar findings from Scandinavia were demonstrated by Paavonen et al. (99). In the United States, Wasserheit et al. (44) noted that anaerobic and aerobic bacteria were recovered from the upper genital tract in 44% of patients with acute PID. Brunham et al. (101) in a Canadian study, and Soper et al. (102), in a United States study, reported a lower recovery of mixed anaerobic and facultative bacteria from the fallopian tubes, with rates of 20% and 13%, respectively. However, Soper et al. (102) noted that anaerobic and facultative organisms were isolated from the endometrial cavity in 31.4% of their laparoscopically confirmed cases of PID. Hillier et al. (103) recently reported that anaerobic and aerobic bacteria were recovered from the fallopian tube in 50% and the endometrial cavity in 94% of acute PID cases. In addition, Paavonen et al. (192) reported that significant enterobacterial common antigen and *B. fragilis* antibody titers were present in one third of patients with PID, supporting the concept that anaerobes and aerobes are involved in the etiology of PID.

Study	No. of Patients	Chlamydia trachomatis	Neisseria gonorrhoeae	Anaerobic and Aerobic Bacteria
Sweet et al. (3,43,45,141)	388	69 (18%)	172 (45%)	267 (70%)
Wasserheit et al. (44)	23	11 (44%)	8 (35%)	11 (44%)
Heinonnen et al. (100)	25	10 (40%)	4 (16%)	17 (68%)
Paavonen et al. (99)	35	12 (34%)	4 (11%)	24 (69%)
Brunham et al. (101)	50	21 (42%)	8 (16%)	10 (20%)
Soper et al. (102)	84[a]	1 (1.2%)	32 (38%)	12 (13%)
	51[b]	6 (12.4%)	48 (98%)	16 (32%)
Hillier et al. (103)	85[c]	3 (4%)	16 (19%)	43 (50%)
	178[c]	23 (13%)	44 (25%)	168 (94%)

[a] Fallopian tube(s)-ovary.
[b] Endometrial cavity.
[c] Landers DV, et al.

TABLE 14.10. RECOVERY OF MICROORGANISMS FROM THE UPPER GENITAL TRACT OF PATIENTS WITH ACUTE PELVIC INFLAMMATORY DISEASE

It is apparent that many of these nongonococcal, nonchlamydial microorganisms have been implicated in BV, a complex synergistic vaginal infection associated with *G. vaginalis,* members of the *Prevotella* sp (particularly *P. bivia, P. disiens,* and *Prevotella capillosus*), *Peptostreptococcus* sp, the mobile curved anaerobic rod *Mobiluncus* sp, a-hemolytic streptococci, and *M. hominis* (193,194,195,196 and 197). Eschenbach (27) initially postulated that BV might be an antecedent precursor in the lower genital tract for the development of nongonococcal, nonchlamydial PID.

Several investigations have demonstrated an association between BV and PID (99,102,103,107,198,199,200 and 201). Paavonen et al. (99) reported that 9 (29%) of 31 women with laparoscopically confirmed acute PID had BV, compared with 0 of 14 controls. All nine of these women had histologic endometritis present on endometrial biopsy. Subsequently, Eschenbach et al. (198) noted that women with BV were significantly more likely to have adnexal tenderness (4% vs. 0.3%), uterine tenderness (4% vs. 1%), cervical motion tenderness (3% vs. 0.6%), and a diagnosis of PID (3% vs. 0%) than control women without BV. Hillier et al. (107) reported that the BV-associated microorganisms (*Prevotella, Peptostreptococcus,* and *M. hominis*) were associated with histologic endometritis in confirmed cases of PID. Even after controlling for chlamydial and gonococcal infection, the recovery of BV-associated bacteria from the endometrial cavity was independently associated with histologic endometritis (107). Recently, in women with laparoscopically confirmed PID, Soper et al. (102) noted that BV was present in 61.8%. In addition, all the anaerobes recovered from the upper genital tract in their study were the BV-associated microorganisms (102). Korn et al. (199) noted that 10 (45%) of 22 women with BV had plasma cell endometritis, compared with 1 (5%) of 19 controls. Peipert et al. (200) reported that objective evidence (histologic, microbiologic, or laparoscopic) of upper genital tract infection was present in 14 (56%) of 25 women with a clinical diagnosis of BV, compared with 27 (30%) of 91 without BV ($p = 0.015$). Using logistic regression, the presence of BV was associated with a threefold increased risk of upper genital tract infection (OR, 3.0; 95% CI, 1.2–7.6). Korn et al. (201) more recently demonstrated that plasma cell endometritis was present in 42% of women with BV versus 13% of controls (OR, 6.5; 95% CI, 1.7–3.5). A higher incidence of BV has been noted in women who wear IUDs than among those who do not or those who use other contraceptive methods (202,203). Such an association may play a role in the pathogenesis of nongonococcal, nonchlamydial PID. Bukusi et al. (104) noted that women with PID who are infected with the human immunodeficiency virus (HIV) are more likely to have BV than HIV-1–seronegative women. Whereas *N. gonorrhoeae* and *C. trachomatis* infections were most common in the HIV-1–seronegative group, they were least common among HIV-1–infected women (104).

Fitz-Hugh And Curtis Syndrome

Perihepatitis is the presence of acute right upper quadrant pain and tenderness in association with acute salpingitis. More commonly, this entity is known as the Fitz-Hugh and Curtis syndrome. Usually, the symptoms and signs of this syndrome are preceded by the clinical onset of acute PID. On occasion, though, the right upper quadrant findings occur before the symptoms and signs of PID become apparent. Differentiation from acute cholecystitis may be difficult in such instances. Initially, this syndrome was ascribed as a complication of gonococcal salpingitis. It was estimated that 1% to 10% of patients with gonococcal salpingitis developed perihepatitis (Fitz-Hugh and Curtis syndrome) (204,205). *N. gonorrhoeae* has been rarely isolated from the peritoneal cavity of women with this syndrome (204). Perihepatitis with the Fitz-Hugh and Curtis syndrome has more recently been associated with *C. trachomatis* infection in women with acute salpingitis (206,207,208,209 and 210).

PATHOGENESIS

Most PID cases occur as the result of intracanalicular spread of microorganisms from the endocervix and vagina to the endometrium and fallopian tubes (9). Generally,

10% to 19% of patients with cervical infection due to *N. gonorrhoeae* and *C. trachomatis* will develop PID (4,6,7,26). In a few studies, up to 40% of women who have not been treated for gonococcal or chlamydial cervicitis or who have been exposed to men with gonococcal or chlamydial urethritis develop clinical symptoms of PID (211,212). With the use of endometrial biopsy to detect histologic endometritis, higher percentages of subclinical ascending infection of the upper genital tract are seen in women with gonococcal or chlamydial cervicitis (9). Similarly, ascending infection of the endometrial cavity documented by the presence of histologic endometritis occurs in women with BV (107,199,200 and 201).

In a recent review on PID, the CDC listed four factors that might contribute to the ascension of bacteria from the endocervix and vagina and that might be associated in the pathogenesis of PID (9). These include the following: (a) uterine instrumentation, particularly insertion of an IUD, which facilitates upward spread of vaginal and cervical microorganisms; (b) hormonal changes during menses, as menstruation leads to cervical changes resulting in loss of the mechanical barrier that helps prevent the ascension of bacteria; (c) retrograde menstruation favors the ascension of bacteria from the endometrium to the fallopian tubes and peritoneal cavity; and (d) individual microorganisms have potential virulence factors associated with the development of PID.

For acute PID to develop, ascension of microorganisms from the lower genital tract through the internal cervical os, into the endometrial cavity, through the uterotubal junction, and into the fallopian tubes must occur (4,105,213). This intracanalicular spread of microorganisms is associated with a continuum of infection both microbiologically and histologically that includes the cervix, endometrium, and fallopian tubes (34,214). It is believed the endocervical canal and the cervical mucous plug are the major barriers that protect the upper genital tract from microorganisms present in the vagina and cervix (105,215). Infection of the cervix with *C. trachomatis, N. gonorrhoeae,* or other microorganisms could result in damage to the endocervical canal or breakdown of the cervical mucous plug, thus leading to ascending infection (105). An additional condition that might facilitate the ascension of microorganisms may be damage to the normal clearance mechanisms associated with ciliated epithelial cells in the endometrium and fallopian tube (105). Although such a mechanism has been attributed to *N. gonorrhoeae* and *C. trachomatis,* Soper et al. (102) recently proposed that BV may facilitate the ascension of STD organisms and other aerobes through enzymatic degradation by proteolytic enzymes associated with the BV-associated bacteria. This complex interaction of STD organisms and the endogenous flora of the vagina and cervix is portrayed in Fig. 14.3.

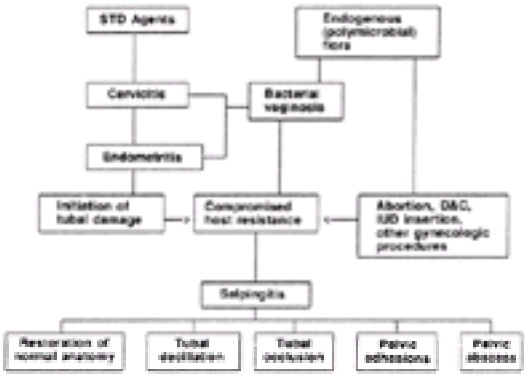


FIGURE 14.3. Possible interrelation of sexually transmitted disease and endogenous organisms in the pathogenesis of pelvic inflammatory disease.

The anatomy and physiology unique to women may combine to facilitate the ascending infection with *N. gonorrhoeae, C. trachomatis,* or endogenous bacteria from the vagina (105,213). As discussed in the previous section on risk factors, young age is a major risk factor for PID. Cervical ectopy occurs more commonly in adolescents and results in a larger target area for attachment of *C. trachomatis* (216,217). Rice and Schachter (105) suggested that other specific age-related changes in cervical mucous or other endocervical defense mechanisms may also play a role in facilitating ascending infection. Hormonal changes associated with the normal menstrual cycle affect the potential for ascending infection via their effect on cervical mucous. At midcycle when estrogen levels are high and progesterone low, cervical mucus may facilitate the ascension of infection, whereas after ovulation, high progesterone levels make the mucus thick and less penetrable to bacteria (105,213). Moreover, with onset of menses, the cervical mucous plug is lost and microorganisms from the vagina and cervix can ascend into the uterine cavity. Interestingly, most symptomatic chlamydial and gonococcal PID cases have their onset during or just after the menses (95,96,218). Retrograde menstruation has been proposed as a mechanism by which microorganisms from the endometrial cavity may be propelled into the fallopian tubes (105).

Whether combination oral contraceptives alter the risk for PID is controversial (82,105). Although women who use oral contraceptives may be at increased risk for cervical chlamydial infection (82,216,217), most studies demonstrate that both the incidence of PID and the clinical and laparoscopic severity of PID are reduced in patients who use oral contraceptives (23,36,80,81,105,219). *In vitro* studies have demonstrated that progesterone inhibits the growth of *N. gonorrhoeae* (220,221,222 and 223). On the other hand, in animal models, estrogen and progesterone appear to facilitate the growth of *C. trachomatis* and the ascension of *C. trachomatis* into the upper genital tract (105). As a result of these studies, Rice and Schachter (105) raised concern about whether oral contraceptives mask the signs and symptoms of ascending infection, leading to an increase of subclinical cases that also are associated with tubal infertility and ectopic pregnancy. Recently, using histologic endometritis as a surrogate for PID, Ness et al. (224) confirmed that this may be the case.

Although the host immune system protects against infection through rapid and efficient clearance of bacteria, the resultant inflammatory response paradoxically may lead to tissue damage or persistent infection (105). For example, secretory immunoglobulin A (IgA) antigonococcal antibody inhibits attachment of *N. gonorrhoeae* to epithelial cells but interferes with phagocytosis of bacteria by polymorphonucleocytes. Similarly, oxygen metabolites such as hypochlorite, superoxide anion, and hydrogen peroxide, which are produced when polymorphonucleocytes phagocytose bacteria, may cause tissue damage to the mucosal surface of the genital tract (225). In addition, the cell-mediated immune response to bacteria, particularly *C. trachomatis,* may result in a pathogenic

mechanism that leads to tissue damage (105).

Gonococcal Pelvic Inflammatory Disease

With *N. gonorrhoeae,* the usual route of infection is thought to be direct canalicular spread of the organism from the endocervix, along the endometrial surface to the tubal mucosa, leading to endosalpingitis. Approximately 10% to 17% of women who acquire endocervical gonorrhea will develop upper genital tract infection (4,6,26).

The menstrual cycle influences the environment of the lower genital tract and may play a significant role in the breakdown of local host mechanisms that normally prevent the ascension of microorganisms from the endocervix. Sixty-six percent to 77% of patients with gonococcal salpingitis present at the end of, or just after, the menstrual period (26,188,218). Using laparoscopy, Sweet et al. (117) demonstrated a dramatic relationship between the menses and gonococcal salpingitis. Although the recovery of the gonococcus from the cervix was most frequent within the first 7 days of the menstrual cycle, it was recovered from the cervix throughout the menstrual cycle. On the other hand, the gonococcus was isolated from the fallopian tubes only within the first 7 days after the onset of menses. Previously, it was postulated that during the menstrual period, the loss of the cervical mucous plug allows microorganisms from the endocervix and vagina to gain access to the endometrial cavity. The bacteriostatic effect of cervical mucus is lowest at the onset of menses. Additionally, the endometrium, which may offer local protection against bacterial invasion, has been sloughed. Menstrual blood from the endometrial cavity is an excellent culture medium. It has been postulated that the gonococci either migrate into the fallopian tubes or are carried there with refluxed menstrual blood. Another possible mechanism, suggested by Toth et al. (226), may be the transport of gonococci via sperm attachment to the fallopian tubes. However, no data have been presented *in vivo* demonstrating that such a mechanism exists or that sperm can actually bring bacteria into the upper genital tract. In addition, isolation rates of *N. gonorrhoeae* from the fallopian tubes in patients with acute salpingitis are inversely related to the duration of symptoms (3,108,125). Whether this observation is due to an inability of *N. gonorrhoeae* to survive in the upper genital tract in the face of endogenous bacteria ascending into the upper genital tract or that gonococcal infection produces rapid onset of severe symptoms leading to quickly seeking health is unclear (3).

Studies using human fallopian tube organ cultures have shown that as gonococci reach the endosalpinx, they become attached to mucosal epithelial cells, penetrate the epithelial cells, and cause cell destruction (178,227,228). Within 2 to 7 days, ciliary motility is lost in fallopian tube organ cultures inoculated with *N. gonorrhoeae,* Gonococci selectively attach to and invade the nonciliated mucus-secreting cells of the fallopian tube epithelium (227,228). Gregg et al. (29) reported on the production of an endotoxin (lipopolysaccharide) by the gonococcus, which damages ciliated cells in human fallopian tube organ culture systems. A second structural component of the surface of *N. gonorrhoeae,* peptidoglycan, has also been shown to damage the fallopian tube mucosa (229).

Additional pathogenic mechanisms have been demonstrated for *N. gonorrhoeae.* Gonococci produce IgA proteases that break down secretory IgA, which binds to microorganisms and prevents their adherence to mucosal surfaces (230). Consequently, adherence of gonococci to mucosal cells is facilitated. *N.*

gonorrhoeae organisms also produce extracellular products such as phospholipase and peptidase, which can lead to cellular damage (105). *N. gonorrhoeae* infection induces the production of interferon gamma (IFN-g), which in turn induces expression of major histocompatibility complex (MHC) Class II/IA antigens on epithelial cells. Expression of Class IA results in activation of both the humoral and the cell-mediated immune response that is directed against these epithelial cells (105). This immune response may be another mechanism by which *N. gonorrhoeae* destroys fallopian tube epithelial cells infected with the organism (105,231). Grifo et al. (231) demonstrated that IFN-g was present in the serum in 65% of women with acute PID, compared with 0% of healthy female controls.

Inherent properties of *N. gonorrhoeae* may also determine its ability to produce upper genital tract disease. It has been postulated that there are different strains of gonococci and that a particular strain or strains may be associated with the development of salpingitis. This concept holds for disseminated gonorrhea in which the strain producing disseminated disease varies by microbiologic susceptibility patterns and auxotypes from the organism, causing asymptomatic lower genital tract disease. Draper et al. studied several potential virulence factors in paired fallopian tube–peritoneal cavity and endocervical isolates of *N. gonorrhoeae* obtained from patients with acute PID undergoing laparoscopy. Specifically, auxotypes (nutritional requirements), antimicrobial susceptibility, serum bactericidal activity, and colony phenotype were studied (232,233). Similar to the finding with disseminated gonorrhea, the gonococci recovered from women with PID had significantly different auxotypes and antimicrobial susceptibility patterns, compared with those in uncomplicated anogenital disease. In contradistinction to the findings with disseminated gonorrhea, the gonococci causing acute PID were relatively more resistant to multiple antimicrobial agents, and the auxotype pattern most associated with acute PID was the prototrophic pattern (i.e., no extra amino acids required for growth), whereas the arginine-hypoxanthine-uracil auxotype pattern was associated with uncomplicated lower genital tract gonorrhea. However, there was no difference among paired peritoneal cavity–cervical isolates of *N. gonorrhoeae* recovered from patients with salpingitis relative to auxotypes and antimicrobial susceptibility patterns. The potential virulence factor that was significantly different in the paired fallopian tube–endocervical gonorrheal specimens was colony phenotype (232). The organisms in the fallopian tube of women with acute salpingitis tended to be the transparent colony phenotype, whereas those present in the cervix of the same women tended to be opaque. In previous studies, women cultured during the menstrual cycle, except during the time of the menses, had a preponderance of opaque organisms isolated, with a peak at the time of ovulation. The organisms usually recovered from the male urethra are heavily opaque, and the organisms recovered from women who use oral contraceptives are opaque (women who use oral contraceptives appear to be protected against the development of upper genital tract disease if they acquire gonorrhea).

Thus, epidemiologically and clinically, it appears that the transparent colony phenotypes may well be the virulent form of the gonococcus in the pathogenesis of acute salpingitis. To test this hypothesis, human fallopian tube and cervical organ culture explant systems were used to evaluate endocervical and fallopian tube attachment. At both the endocervix and the fallopian tubes, the transparent colony phenotype of *N. gonorrhoeae* attaches more avidly to human fallopian tube tissue than their opaque colony phenotype counterparts (234). It appears that something in the cervical milieu (hormones, pH, or an unidentified factor) may either select out the transparent colony phenotype or selectively drive the gonococci from opaque to

transparent forms. The basic difference between the opaque and transparent colony phenotypes are proteins present in the outer cell membrane of the organism (see the section on gonorrhea in Chapter 7 [Sexually Transmitted Diseases]).

As noted by Westrom and Eschenbach (4), immunologic defense mechanisms induced by *N. gonorrhoeae* may provide some protection against recurrent gonococcal PID. In addition to colony phenotype (opaque or transparent), *N. gonorrhoeae* colony types are differentiated by the presence or absence of pili (235,236). The piliated strains appear to be pathogenic (235,236). Using principal outer membrane proteins to serotype the gonococcus, Buchanan et al. (237) demonstrated the presence of nine serotypes of gonococci. They noted that three of the serotypes (1, 2, and 8) were responsible for nearly 75% of gonococcal salpingitis. In addition, these investigators reported that reinfection with a similar serotype of gonococci results in cervical infection but not in fallopian tube infection, whereas reinfection with gonococci of a different serotype results in both cervical and fallopian tube infection. This finding suggests the presence of immunity of the fallopian tube site among previously infected women.

Chlamydial Pelvic Inflammatory Disease

It is generally held that chlamydial salpingitis, similar to the situation in gonococcal salpingitis, results from the intracanalicular spread of *C. trachomatis* from the endocervix to the endometrium and then to the fallopian tube (113,152,238). An estimated 10% of *C. trachomatis* cervical infections ascend to cause PID (4). Ripa et al. (166) showed that *C. trachomatis* in a Grivet monkey model gains access to the fallopian tube mucosa as an ascending intracanalicular infection from the endocervix. Toth et al. (226) reported that *C. trachomatis* attaches to sperm and suggested that sperm may well be the vector that facilitates the spread of microorganisms including chlamydiae into the upper genital tract. However, actual attachment of *C. trachomatis* organisms was not proven. Moreover, no study has demonstrated that sperm can carry *C. trachomatis* into the upper genital tract *in vivo.* Recently, an association between chlamydial salpingitis and menstruation, similar to that for *N. gonorrhoeae,* has been noted (96). In this study, among the women who developed acute PID, 50% of chlamydial infections occurred within 7 days of the onset of menses. Thus, it appears that the pathogenesis of chlamydial salpingitis parallels that seen in gonococcal disease. No specific virulence factors that facilitate the development of acute PID have been identified for *C. trachomatis.*

Scanning and transmission electron microscopy studies have demonstrated that after *C. trachomatis* ascends to the fallopian tube, it attaches to the tubal epithelium and is engulfed via the process of endocytosis in a membrane-lined vacuole (239). As a result *C. trachomatis* replicates within the cell and is protected from recognition by the host immune system (4). Ultimately, the elementary bodies, which are the infectious form of *C. trachomatis,* are released into the tubal lumen, from which additional mucosal cells can be infected (239). *C. trachomatis* has been shown to replicate with inclusion formation in both the ciliated and the nonciliated mucosal cells in human fallopian tube organ cultures (240) and the oviducts of mice infected with mouse *C. trachomatis* (241). In addition, in a nonhuman primate model, Patton (242) demonstrated that both ciliated and nonciliated cells were affected by chlamydial infection.

Unlike the situation with most bacterial infections, in which tissue damage directly

results from bacterial replication and inflammation, the damage and scarring associated with *C. trachomatis* result from the host immune response to the infection (157,158,159,160,161,162,163 and 164,171,172,243,244,245,246 and 247). In a monkey model, Patton et al. (171) demonstrated that primary chlamydial infection is associated with a mild to moderate inflammation with an influx of polymorphonuclear cells. This is a self-limited infection that peaks by 2 weeks and resolves within 5 weeks (171). On the other hand, repeated inoculations with *C. trachomatis* result in an infection and inflammation characterized by mononuclear cells and the formation of lymphoid follicles (171). Rather than a self-limited infection with complete resolution, repeated infection in this monkey model produces extensive tubal scarring, distal tubal obstruction, and peritubal adhesions (172). Such scarring of the fallopian tube subsequently leads to tubal infertility or ectopic pregnancy (105).

Recent investigations have identified a *C. trachomatis*–specific 57-kd protein that is responsible for this inflammatory response (157,158,159,160,161,162,163 and 164,246,247). As noted by Møller et al. (248), the histopathology of the inflammatory response to this 57-kd protein is similar in human fallopian tube tissue to that seen in blinding trachoma and genital tract models of infertility. This 57-kd protein has been identified as an Hsp (105,159,160,161,162,163 and 164) and has been shown to induce a hypersensitivity response. Wager et al. (249) have demonstrated that women with PID or ectopic pregnancy have antibodies against this protein. Similarly, Brunham et al. (250) reported that patients with TFI have antibodies directed at the 57-kd antigen, and Witkin et al. (158) reported that induction of a cell-mediated immune response to the chlamydial 57-kd Hsp is a common feature of upper genital tract infection. Recently, Patton et al. (160) demonstrated that *C. trachomatis* infection in monkeys induced delayed hypersensitivity that is mediated by *C. trachomatis* Hsp 60.

Several investigators have demonstrated that chlamydial infection induces the production of various cytokines, which leads to inflammation and scar formation (251,252 and 253). The cytokines involved are tumor necrosis factor, interferon, and interleukin. Witkin et al. (254) demonstrated that peripheral blood monocytes from patients with acute PID produced increased levels of interleukin-1 and interleukin-6, which are cytokines capable of producing scarring and tissue damage. Further evidence for the role played by the cytokine response to chlamydial infection is the work demonstrating the presence of IFN-g in cervical secretions of women with chlamydial cervicitis (255) and in the serum of women with acute PID (231). The presence of IFN-g may lead to an additional increase in cytokine production and, most importantly, induce expression of the MHC Class II on epithelial cells (4). In turn, expression of MHC Class II–bound antigens on epithelial cells of the fallopian tube probably initiates a cell-mediated immune response directed against the epithelial cells infected with *C. trachomatis,* leading to destruction of the fallopian tube mucosal cells, similar to what occurs in blinding trachoma (256). Thus, the pathogeneses of both acute PID and trachoma due to infection with *C. trachomatis* are similar, with the resultant scarring leading to tubal obstruction and blindness, respectively.

Nongonococcal, Nonchlamydial Pelvic Inflammatory Disease

The pathogenesis of nongonococcal, nonchlamydial PID has not been well studied or elucidated. PID is a polymicrobial infection, and the organisms implicated include aerobic and anaerobic bacteria (1,3,4,109,110). Whether genital tract mycoplasmas,

particularly *M. hominis,* are also putative agents for PID is debated, as discussed later in this chapter. Also, as described already, various facultative and anaerobic bacteria have been recovered alone or in combination with *N. gonorrhoeae* or *C. trachomatis* from the upper genital tract of women with acute PID (3,4,97,98,106,107,109,120,123,257). Most frequently, these bacteria are comprised of endogenous vaginal microflora. However, respiratory pathogens such as *Haemophilus influenzae, Streptococcus pneumoniae,* and group A b-hemolytic streptococcus have been isolated from the fallopian tubes of women with acute PID (97,98,102,108). Typically, multiple bacteria are recovered from patients with acute PID. This finding was the basis for the concept of “polymicrobial” PID initially coined by Eschenbach et al. (97).

The cervix and vagina of healthy women have been shown to contain a multitude of aerobic and anaerobic bacteria (258). How these organisms gain access to the upper genital tract has not been clearly defined. As postulated for *N. gonorrhoeae,* they may reach the fallopian tube in menstrual blood reflux or attach to sperm and then be carried to the fallopian tubes. Eschenbach and Holmes (26) suggested that there may be a critical number of organisms needed to overwhelm local host defense mechanisms in the cervix, thereby allowing an infection to ascend to the upper genital tract.

It seems likely that there is a continuum from the entity of BV, which is associated with significantly increased and very high colony counts of anaerobic bacteria and *G. vaginalis* and nongonococcal, nonchlamydial acute PID. Many of the nongonococcal, nonchlamydial microorganisms recovered from the upper genital tract of women with acute PID are the same as those associated with BV (BV-associated organisms) (3,4,43,99,102,106,107,259). In addition to the microbiologic studies linking acute PID and BV, Eschenbach et al. (198) demonstrated that young women with BV were significantly more likely to have symptoms and signs associated with acute PID and to be diagnosed with acute PID than matched controls without BV. Most recently, several investigations have confirmed an association between BV and histologic endometritis in women with clinical signs and symptoms of acute PID (199,200). A hypothesis that requires confirmation is that the synergistic infection with anaerobes and *G. vaginalis* may be a third (in addition to *N. gonorrhoeae* and *C. trachomatis*) instance in which a lower genital tract infection ascends into the upper genital tract and produces acute salpingitis. Even if such a hypothesis is not confirmed, it is apparent that nongonococcal, nonchlamydial bacteria are involved in the etiology and pathogenesis of acute salpingitis (3,4,109,260). Westrom and Eschenbach (4) pointed out the current inadequate state of knowledge about how or under what circumstances endogenous vaginal bacteria produce infection in a healthy fallopian tube or if facultative and anaerobic bacteria can only infect fallopian tubes that have been “primed or compromised” by an earlier process. Thus, whether the pathogenesis of gonococcal, nonchlamydial acute PID involves an ongoing dynamic process initiated by ascending infection with *N. gonorrhoeae* or *C. trachomatis* followed by a superimposed polymicrobial stage or whether endogenous vaginal microorganisms ascend primarily into the upper genital tract to produce infection without preexisting cervical or upper genital tract infection with *N. gonorrhoeae* or *C. trachomatis* is debated. That endogenous vaginal microorganisms can be primary pathogens is demonstrated by the laparoscopy study of Sweet et al. (125), in which nongonococcal, nonchlamydial organisms caused acute salpingitis without antecedent infection with *N. gonorrhoeae* or *C. trachomatis.* Similarly, recent studies have demonstrated the presence of facultative and anaerobic bacteria in the endometrium of patients with PID but without evidence of *N. gonorrhoeae* or *C.*

trachomatis (41,107). Although not identified yet, some alteration in the normal cervical defense mechanism must occur to allow microorganisms from the cervix and vagina to gain access to the upper genital tract. Perhaps cervical infection with *N. gonorrhoeae* or *C. trachomatis* produces such a change. Soper et al. (102) suggested that BV might facilitate the ascension of chlamydial and gonorrheal infections. On the other hand, the metabolic by-products and enzymes produced by vaginal bacteria could alter the cervical mucous and facilitate ascending infection.

The pathogenic mechanism of IUD-associated salpingitis is different from that seen with the gonococcus or chlamydia. When the IUD was reintroduced into clinical practice in 1959, it was postulated that infection would occur only at the time of insertion, with a break in sterile technique, or with the introduction of pathogenic bacteria. More recently, it has become apparent that the device alters the host defense mechanisms within the uterine cavity. There are various ways in which an IUD can interfere with normal host defense mechanisms. These include (a) breakdown of the mucosal surface in the endometrial cavity; (b) foreign body interference with the ability of polymorphic neutrophils to phagocytose bacteria; (c) development of a biofilm that protects bacteria from host defenses; (d) decreased concentration of bacteria required to produce infection; and (e) presence of minerals that can interfere with some components of the host defenses. In addition, recent studies have shown that the IUD string facilitates upward spread of bacteria, which allows organisms to ascend to the lower uterine segment (74,75). This combination of the string facilitating ascension of bacteria from the lower genital tract and the presence of a foreign body interfering with local host defense mechanisms sets the stage in the uterine cavity for the development of endometritis and subsequent progressive endometritis, leading to salpingitis. These patients usually present with intermenstrual bleeding and cramplike abdominal pain. Histologically, there are submucosal microabscesses beneath the area of the IUD placement (261). Ober et al. (262) demonstrated that IUD wearers with symptoms of bleeding and cramplike abdominal pain were significantly more likely to have histologic endometritis than asymptomatic IUD users. More recently, in the PEACH study, we confirmed that IUD use is significantly associated with histologic endometritis in patients with acute PID (78). Once endometritis is established, the pathogenesis of infection is similar to that seen with non-IUD-associated acute PID. Although it was previously believed that IUD infections were similar to postabortion or postpartum infections in which bacteria ascend via lymphatics in the parametrial tissue and broad ligament to reach the tube and adnexa, producing a perisalpingitis, it is now believed that direct spread of microorganisms from the infected or colonized uterine cavity to the fallopian tubes is the major pathogenic mechanism. It has been suggested that women with acute salpingitis in association with the IUD are at increased risk for the development of adnexal abscesses (261). n addition, it was felt that these IUD infections tend to be unilateral, compared with other types of PID, which tend to be bilateral. Landers and Sweet (257) reported that 70% of their series of 232 patients with tuboovarian abscesses (TOAs) were unilateral; this was true for IUD users and non-IUD users. Thus, it appears that there is not an association between IUD use and unilateral adnexal infection. One pelvic infection that is unique to IUD use is that due to *Actinomyces israelii.* This organism is associated with severe infection and extensive inflammatory response, particularly abscess formation and fistula formation. Women who use IUDs are at increased risk to have colonization (documented by Papanicolaou smear) with *A. israelii* in the lower genital tract.

THE INFLAMMATORY PROCESS

As a result of the inflammatory reaction associated with ascending infection reaching the fallopian tube, vasodilation, transudation of plasma, and migration of cellular elements into tissue occur (213). With *N. gonorrhoeae* and facultative and anaerobic bacteria, an acute neutrophilic inflammatory response occurs with destruction of the endosalpinx and production of a purulent exudate. In the early stages of the disease, the tubal lumen is open, and the purulent material exudes from the fimbriated end of the tube, resulting in pelvic peritonitis. As a result of the peritoneal inflammation, contiguous pelvic structures such as the ovary, omentum sigmoid, small bowel, broad ligament, and cecum become involved in the process. In an attempt to protect the upper abdomen and ward off the source of peritoneal contamination, the fimbriated end of the tube may become blocked with the resultant development of an acute pyosalpinx. If the ovary becomes involved in the infectious process, the result is a TOA.

In association with the inflammatory process, there is concurrent tissue repair underway consisting of removal of dead cells and ingrowth of fibroblasts, resulting in scar formation and impairment of tubal function (213). All three layers of the fallopian tube (interstitial, muscular, and serosal) may be involved. When the serosal layer is involved, an inflammatory exudate occurs on this peritoneal surface, which can become organized and adhere adjacent surfaces to each other. As a result of this inflammatory process, deciliation of tubal epithelium, intraluminal adhesions, tubal occlusion, and peritubal adhesions occur (3). These anatomic changes lead to infertility and ectopic pregnancy.

Infection with *C. trachomatis* is associated with a more indolent cell-mediated immune response, which has been described already. The severe inflammation seen with *C. trachomatis* (particularly repeated infection) results from an immune response to chlamydial Hsp 60 (159,160 and 161).

PID SEQUELAE

Despite prompt diagnosis and treatment, acute PID is associated with significant sequelae that have a profound adverse impact on the general and reproductive health of young women (3,4,9,17,32,263,264,265,266,267,268 and 269). These include short-term consequences such as perihepatitis (Fitz-Hugh and Curtis syndrome), TOA, and rarely mortality. Of greatest concern, long-term sequelae develop in approximately 25% of women with acute PID (270). These include infertility, ectopic pregnancy, and chronic pelvic pain (259,271,272). In addition, recurrent PID is frequently seen. Similar sequelae have also been associated with “unrecognized” or “silent” PID (21). The adverse impact on reproductive health has been recoginzed since the report by Noeggerath (273) nearly 125 years ago describing the influence of latent gonorrhea on fertility (273).

Mortality as the result of acute PID has not received much attention. The death to case ratio for PID is very low (7,270,274), so mortality is not viewed as a major problem in PID in industrialized nations. However, using vital statistics records, Grimes (274) reported that in 1979 in the United States, the mortality rate for PID was 0.29 per 100,000 women aged 15 to 44 years, which translates to one death

due to PID occurred every other day in the United States. Rupture of a TOA with resultant generalized peritonitis is the most frequent cause of mortality associated with PID (275,276). With rupture and severe peritonitis, mortality rates range from 3% to 8% (275,276).

Perihepatitis (Fitz-Hugh and Curtis syndrome) is a clinical syndrome characterized by acute right upper quadrant pain and tenderness in association with acute PID. It is estimated to occur in 1% to 10% of patients with acute PID (204,205). TOA is a severe inflammatory consequence of PID in which the ovary and fallopian tube coalesce into an inflammatory mass. TOA is reported to occur in 7% to 16% of hospitalized cases of acute PID (257). TOAs are discussed in greater detail in Chapter 8 (Mixed Anaerobic-Aerobic Infection and Pelvic Abscess).

Infertility

The most important and most common long-term complication of acute PID is TFI (7,263,267). In Sweden, Westrom et al. (263) conducted the most comprehensive prospective studies, which reported the results of a large cohort of all women treated for PID at the University Hospital in Lund, Sweden, between January 1, 1960, and December 31, 1984. During this time, 2,501 women underwent diagnostic laparoscopy with a suspected diagnosis of acute PID; 1,844 had acute PID and 657 had normal findings (control group). The reproductive events of 1,732 patients with PID and 601 controls were followed. There were 1,309 PID cases and 451 control patients who attempted to conceive during the follow-up period. Of those followed, 209 of PID cases (16%), compared with 12 controls (2.7%), failed to become pregnant. Confirmed (laparoscopy, hysterosalpingogram [HSG] or laparotomy) TFI was documented in 141 patients with PID (10.8%) and none of the controls. If women with incomplete infertility workups but who had morphologically abnormal fallopian tubes are included, the rates of TFI in patients and controls was 12.2% (165 of 1,362) and 0.9% (4 of 457), respectively. The rate of infertility was directly associated with the number of episodes of PID (Table 14.11) and the severity of PID at laparoscopy. Each subsequent episode of acute PID approximately doubled the rate of TFI, rising from 8.0% with one episode to 19.5% with two episodes and 40.0% with three or more episodes (Fig. 14.4) (264). Among women with one episode of PID, the rate of TFI was 0.6% for mild, 6.2% for moderate, and 21.4% for severe PID (264). Oral contraceptive users had significantly less severe PID (16.9%) than women using no contraception (25.9%) or women using other methods of contraception (264). In addition, women with PID who used oral contraceptives had lower rates of TFI, 3.7% versus 11.8% for those who do not use contraceptives, 10.5% for barrier users, 5.4% for IUD users, and 8.7% for users of other types of contraceptives.

Category	Total Women	Infertile		Ectopic Pregnancy		Intrauterine Pregnancy	
		No.	Rate	No.	Rate	No.	Rate
Controls	448	9	2%	6	1%	433	97%
Patients with PID							
First episode	1,035	112	11%	81	8%	852	82%
Second episode	198	70	35%	24	12%	124	63%
Three or more episodes	69	30	43%	15	22%	24	35%

Source: From Westrom LV, Mårdh PA. Consequences of pelvic inflammatory disease. In: Mårdh PA, Westrom LV, eds. Pelvic inflammatory disease. New York: Raven Press, 1982:107–114, with permission.

TABLE 14.11. REPRODUCTIVE FUNCTION AMONG PATIENTS WITH PELVIC INFLAMMATORY DISEASE (PID) AND CONTROLS IN THE PROSPECTIVE LUND STUDY BY PID EPISODE

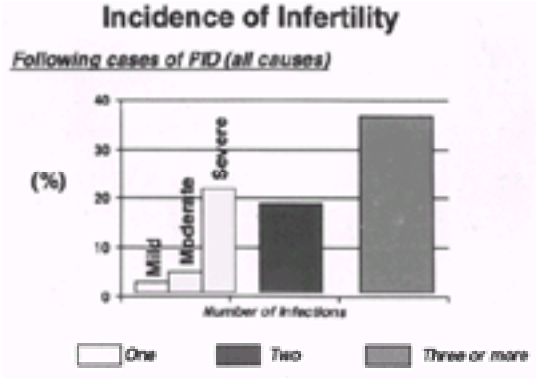


FIGURE 14.4. Incidence of infertility after cases of pelvic inflammatory disease: number of episodes and severity of fallopian tube disease at laparoscopy.

A more recent analysis of data from the Lund, Sweden, cohort demonstrated that the absolute number of episodes may be less important than the disease severity of the initial episode (277). The cumulative proportion of women achieving a livebirth after 12 years was 90% with mild, 82% with moderate, and 57% for severe PID (277). Subsequent episodes of PID in the group with mild PID did not diminish their long-term probability of livebirth. On the other hand, repeated episodes significantly decreased the probability of livebirth in women with severe PID; the risk of failure to achieve a livebirth was increased nearly 5 (relative risk, 1.7 to 8.1) (277). In fact, women with severe disease and subsequent episodes were eight times more likely to not have a livebirth, compared with women with one episode of mild disease (relative risk, 8.1; 85% CI, 3.0–22.2) (277). Further analysis of the Lund data has demonstrated that delayed treatment resulted in poorer outcome; the infertility rate was 19.7% when symptoms were present 3 or more days versus 8.3% when treatment was initiated less than or equal to 2 days from the onset of symptoms (83).

No other large cohort of patients with PID have been followed long term to determine outcomes. In Canada, Brunham et al. (101) confirmed the diagnosis of PID in 50 women who were evaluated 1-year posttreatment for fertility. Among the women attempting to conceive, the infertility rate was 30%. All the women with gonococcal PID who wanted to conceive were successful. On the other hand, infertility was present in 7 (54%) of 13 patients with nongonococcal PID; abnormal HSGs were present in three of the chlamydia-infected patients and four of those with tubal abscess presumed due to anaerobic bacteria. In the United States, Safrin et al. (266) performed a retrospective cohort study of 140 women hospitalized for the treatment of acute PID who were evaluated at a median of 37 months later. These authors reported that 40% of the women with PID were involuntarily infertile (266). Similar to the finding by Hillis et al. (83), Safrin et al. (266) noted that longer duration of abdominopelvic pain before treatment was associated with increased risk of infertility; women who had 2 or more days of symptoms before admission had a twofold increased risk of infertility when compared with women who had pain for less than 2 days (54% vs. 14%; $p = 0.02$). In a small prospective study in the United States, Soper and Ness (269) reported that 55.6% (10 of 18) of their cohort of women with laparoscopically confirmed acute PID were involuntarily infertile after at least 1 year of follow-up.

In an attempt to provide a short-term follow-up alternative to long-term cohort studies, investigators have used second-look laparoscopy several months after treatment of acute PID (278,279 and 280). These studies have shown that peritubal adhesions are present in 35% to 48% and fallopian tube occlusion is present in 3% to 25%. These studies only reflect morphologic and mechanical events but do not assess function (i.e., subsequent fertility).

Retrospective seroepidemiologic studies have demonstrated a strong and consistent association between previous chlamydial infection (i.e., presence of anti-chlamydial immunoglobulin G [IgG] antibody) and TFI (267). These numerous studies are described in detail in Chapter 5 (Chlamydial Infections). In summary, antichlamydial IgG antibodies were present in 57% to 86% of women with TFI, compared with 0% to 25% among those with no tubal disease or with other causes of infertility (79,144,145,146,147 and 148,150,152,281). In most of these studies, the relative risk of TFI associated with past infection with *C. trachomatis* was 3 to 4. However, Reiners et al. (282) reported a relative risk of 7.8 (95% CI, 3.2–19.1) after adjusting for age. As discussed earlier, chlamydial Hsp is believed to play an important role in TFI, by inducing a delayed hypersensitivity response (cell-mediated immune response) (159,160,161,162,163 and 164,283). In one study, 84% of women with TFI had chlamydial Hsp 60 antibodies, compared with 20% of controls (prenatal patients) (284). Of critical importance was the recognition that most women with TFI and antichlamydial IgG antibodies reported no history of a diagnosis or treatment of PID. This finding led to the concept of “unrecognized” or “silent” PID (21), an entity as likely to result in TFI as clinically apparent PID (285).

The role of other organisms and TFI has been infrequently studied, primarily because of the lack of specific and sensitive serologic tests for *N. gonorrhoeae,* genital mycoplasmas, and the BV-associated anaerobic-aerobic bacteria. Limited data from western Europe and Africa demonstrate a high prevalence of antibodies to *N. gonorrhoeae* and *M. hominis* among women with TFI, similar to those seen for *C. trachomatis* (286,287,288,289,290,291,292 and 293). No studies have been reported

on the risk of long-term sequelae associated with PID caused by the BV-associated bacteria, particularly the anaerobes.

Ectopic Pregnancy

Post-PID damage to the fallopian tube is a well-documented cause for tubal ectopic pregnancy (264,294,295 and 296). This may be an underestimate. Cumming et al. (296) reported that when the entire fallopian tube was thoroughly examined histologically, all (eight of eight) had evidence of ongoing low-grade salpingitis or postinflammatory endosalpingeal disorganization in areas away from the ectopic pregnancy. In the cohort study from Lund, Sweden, ectopic pregnancy occurred in the first pregnancy after the index laparoscopy in 9.1% of PID cases, compared with 1.4% of controls ($p < 0.0001$) (263). Similar to what is seen with TFI, a direct relationship between the number of episodes of PID and ectopic pregnancies was seen (Table 14.11). The ectopic pregnancy rate was 6%, 12%, and 22% for one episode, two episodes, and three or more episodes, respectively (263). In a retrospective study in the United States, Safrin et al. (266) reported that among 51 women hospitalized and treated for acute PID and followed for a median of 37 months, 2.4% had an ectopic pregnancy. This is an approximately eightfold increase over the rate of ectopic pregnancy in the general U.S. population of reproductive-age women. In a large British cohort study involving 1,355 women hospitalized with acute PID, Buchan et al. (268) reported that women with PID were ten times more likely than control patients to have had an ectopic pregnancy subsequently—very similar results to those reported by the Swedish cohort study (263). Hillis et al. (293) demonstrated that repeated chlamydial infection increases the risk for ectopic pregnancy. Women with two infections had a 2.5-fold increased risk, compared with those with a single infection, and women with three or more infections had a fivefold increased risk for ectopic pregnancies (293).

Similar to studies of TFI, retrospective seroepidemiologic studies have demonstrated a significant association between ectopic pregnancy and previous chlamydial infection (presence of antichlamydial IgG antibody) (87,154,155,297,298,299,300,301,302 and 303). Chlamydial serologic status has been correlated with tubal histopathology in ectopic pregnancies (299,300 and 301). Brunham et al. (300) demonstrated a relationship between chlamydial seropositivity and plasma cell infiltrates in the tube in cases of ectopic pregnancy, compared with tubal ligation controls (OR, 7.2; 95% CI, 1.7–31). Not only did Sheffield et al. (301) report that pelvic damage was associated with chlamydial seropositivity (OR, 4.2; 95% CI, 1.8–9.7) in cases of ectopic pregnancy, but they also noted that moderate and severe pelvic damage was more strongly associated with positive chlamydial serology than mild damage. Studies by Wagar et al. (249) and Brunham et al. (300) have shown that women with PID who have antibody to chlamydial Hsp 60 are at higher risk of developing ectopic pregnancy. Similar to TFI, the cell-mediate immune response to chlamydial Hsp 60 is probably responsible for the tubal damage.

Because of limited sensitivity and specificity, a limited number of seroepidemiologic studies have addressed the role of nonchlamydial microorganisms in ectopic pregnancy. A few reports from Europe and Africa have shown an association between *N. gonorrhoeae* and mycoplasmas and ectopic pregnancies (291,292,303). There have been no studies assessing the role of BV-associated organisms and anaerobes with ectopic pregnancy.

Chronic Pelvic Pain

Although a fairly common outcome of acute PID, chronic pelvic pain as a sequelae of PID has not been extensively studied. The cause of chronic pelvic pain is usually due to the presence of pelvic adhesions resulting from the inflammatory response to acute PID (267). Falk (113) reported that chronic pelvic pain occurred in 17% of women after diagnosis and treatment of acute PID. In the Lund study, Westrom et al. (265) noted that chronic pelvic pain lasting more than 6 months was present in 18% of laparoscopically confirmed cases of PID, versus 4% of controls. Safrin et al. (266) reported that chronic pelvic pain for 6 or more months occurred in 24% of women hospitalized for treatment of PID. In the large British follow-up study of hospitalized cases of PID, Buchan et al. (268) noted that PID cases were ten times more likely to be admitted later for abdominal pain, four times more likely for gynecologic pain, and eight times more likely to have a hysterectomy. In a Swedish cohort study, similar to other sequelae of PID (e.g., infertility and ectopic pregnancy), the severity and number of episodes of PID were directly proportional to the rate of chronic pelvic pain (265). Chronic pain was present in 12% after a single episode of PID and rose to 67% of women with three or more episodes of PID (265). Westrom and Svensson (304) reported that 88% of post-PID women with chronic pelvic pain had morphologic changes of the fallopian tubes or ovaries at second-look laparoscopy. These authors demonstrated that chronic pelvic pain was highly correlated with the extensiveness of post-PID adhesions (304).

DIAGNOSIS

Acute PID presents with a broad spectrum of manifestations that include unrecognized and overt infection (Fig. 14.5). As noted by Westrom and Eschenbach (4), different clinical presentations, ranging from mild to severe, tend to be associated with different etiologic agents. The specificity of any single clinical or laboratory diagnostic finding is low, so no symptom or sign is pathognomonic of acute PID (4). Approximately two thirds (range, 30% to 75%) of infertile women with postinfection-associated TFI report no history of prior PID (146,151,265,305,306). As a result, it appears that subclinical (unrecognized) infection is responsible for most PID and tubal infertility post-PID. In contradistinction, up to one third of patients presenting with abdominal or pelvic pain presumed to be acute PID are found to have either other conditions (e.g., appendicitis, ectopic pregnancy) or no disease at all (4,113,115,307,308,309,310 and 311). Overt PID ranges from mild to severe clinical presentation. According to Westrom and Eschenbach (4), most laparoscopically confirmed cases of acute PID present with mild to moderate symptoms and signs (Fig. 14.5).

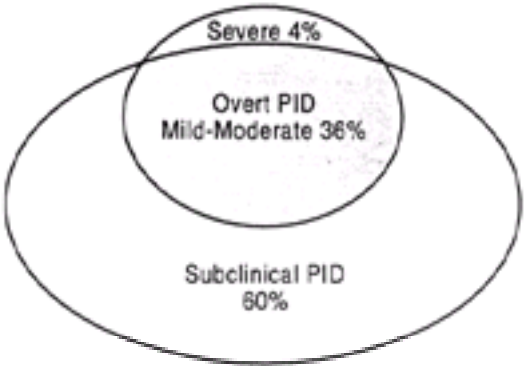


FIGURE 14.5. Proportions of clinical manifestations of pelvic inflammatory disease.

Unrecognized Disease (Atypical PID, “Silent” PID)

It has become clear that many women with PID demonstrate mild, vague, or subtle symptoms that are not recognized by clinicians as PID (4,9,21). This led to Wolner-Hanssen et al. (21) proposing the concept of “silent,” atypical, or unrecognized PID. Such patients with apparent unrecognized infection in retrospective studies of post-PID sequelae often gave no history of having been diagnosed or treated for PID (21). Further support for the concept of unrecognized PID comes from studies demonstrating the presence of inflammation or microorganisms in the endometrium and fallopian tubes of women with few or no symptoms of overt acute PID (305,306,312,313 and 314). Smith et al. (306) demonstrated the presence of plasma cells in the fallopian tubes of asymptomatic women undergoing laparoscopy tubal ligation in 47% of IUD users, versus 1% in women who never used an IUD. Paavonen et al. (312) noted that histologic endometritis was present in 45% of all women with mucopurulent cervicitis and 65% of patients with chlamydial cervicitis. Although none of these patients had the traditional signs of acute PID, abnormal uterine bleeding and mild uterine tenderness were present in many. *C. trachomatis* has been recovered (by culture) by Cleary et al. (313) from the endometrium in approximately 25% of infertile women with antichlamydial IgG antibody and from the fallopian tube by Henry-Souchet et al. (314) in 15% of infertile women with no clinical or laparoscopic evidence of acute PID. Additional evidence for the role of unrecognized disease comes from studies documenting that chlamydial infection persists in the absence of symptoms in the fallopian tubes (31,315,316) and endometrium (43) after treatment of acute PID. Moreover, Patton et al. (285) noted that the pathologic damage in the fallopian tubes secondary to PID was unrelated to whether there was a history of overt infection or absence of any history of clinical symptoms. The concept that ascending infection in the absence of clinical signs and symptoms can result in impaired tubal function and infertility has been widely accepted. However, Wolner-Hanssen (317) voiced a word of caution and suggested that rather than “silent” or subclinical infection, these women had symptoms that were unrecognized as being associated with PID. When assessed with a detailed, focused interview, 60% of women with fallopian tube occlusion but no history of PID reported medical visits for symptoms such as abdominal pain (317).

Overt Clinical Disease

Overt clinically apparent PID can present with symptoms ranging from mild to severe. Traditionally, overt PID was believed to present with lower abdominal pain, purulent cervical discharge, cervical motion tenderness, adnexal tenderness, and fever and leukocytosis. With mild to moderately severe PID, the patient's general condition is good (4). Pain is present in the lower abdomen or pelvis, is continuous, dull, bilateral (usually), and subacute evolving over 48 to 72 hours. Gastrointestinal symptoms such as nausea and vomiting are infrequent with mild to moderate infection and dysuria is noted in 20% (115). In patients with gonococcal or chlamydial PID, the onset of symptoms occurs predominantly at the end of or just after menses (96).

The clinical presentation of severe PID is more characteristic of the classic textbook description of acute PID. However, severe disease accounts for only 5% to 10% of overt PID cases (4). Westrom and Eschenbach (4) divided severe PID into two major groups: (a) young patients with peritonitis, usually associated with *N. gonorrhoeae* and (b) patients 25 years of age or older with TOAs and non-STD–associated PID. Typical severe disease presents after a short duration of symptoms with fever, chills, nausea, and vomiting. Abdominal guarding and rebound consistent with peritonitis is often present. The white blood cell (WBC) count, the ESR, and the C-reactive protein (CRP) level are all elevated in most cases.

Laparoscopy has shown that the diagnosis of acute salpingitis based on these clinically accepted criteria is often inaccurate and unsatisfactory (115). Insistence on such rigid criteria as fever, leukocytosis, elevated ESR, and adnexal masses may result in many more cases of salpingitis being misdiagnosed or inappropriately treated. In 1969, Jacobson and Westrom (115) challenged the accepted clinical diagnosis of acute salpingitis with their objective data based on laparoscopic visualization. Of 814 women who underwent laparoscopy for presumed diagnosis of acute salpingitis (low abdominal pain, cervical motion tenderness, and increased WBC counts on wet mount of vaginal secretions), only 512 (65%) had visual confirmation of the diagnosis (tubal erythema, swelling, and exudate), 184 (23%) had normal pelvic findings, and 98 (12%) had other pelvic pathology, including acute appendicitis, endometriosis, ruptured ovarian cysts, or ectopic pregnancy. Subsequent studies have confirmed that the accuracy of a clinical diagnosis based on the findings of cervical, uterine, and adnexal tenderness in women with abdominal pain is only about 65% (Table 14.12). However, studies performed in the United States have confirmed (with laparoscopy) the presence of salpingitis in 80% to 90% of patients with presumed acute PID (102,117,318).

	Jacobson and Westrom [15] (n = 14)	Chapuro et al. [29] (n = 223)	Sweet et al. [17] (n = 45)	Rosenfeld et al. [44] (n = 36)	Heinonen et al. [100] (n = 30)	Kinlat et al. [142] (n = 55)	Soper et al. [102] (n = 162)	Eschenbach [29] (n = 55)	Bukusi et al. [104] (n = 148)
Salpingitis	65%	49%	85%	83%	69%	62%	82%	82%	91%
Normal pelvis	21%	21%	–	39%	–	–	18%	18%	–
Other diagnoses[a]	13%	31%	11%	–	31%	38%	–	–	10%

[a]Includes appendicitis, ectopic, ovarian cysts, and endometriosis.

TABLE 14.12. LAPAROSCOPIC FINDINGS IN PATIENTS WITH CLINICAL DIAGNOSIS OF ACUTE PELVIC INFLAMMATORY DISEASE

Evaluation of the symptoms and signs in the laparoscopic study of Westrom and Jacobson failed to identify clinical factors that can reliably differentiate between patients with acute salpingitis and a visually normal group. A comparison of symptoms presented by the patients with a normal pelvis, as opposed to those with confirmed salpingitis at laparoscopy, revealed no significant difference in the incidence of lower abdominal pain, increased vaginal discharge, irregular bleeding, urinary symptoms, or gastrointestinal symptoms (Table 14.13). The only significant difference noted was a history of fever and chills in patients with documented salpingitis. However, only 40% of the patients with laparoscopically confirmed salpingitis give a history of fever and chills. Evaluation of the clinical signs or laboratory data on admission did reveal significant increases in the incidence of adnexal tenderness, elevated ESR, fever, and abnormal vaginal discharge in patients with visually confirmed salpingitis (Table 14.14). However, the overlap between the visually normal and the acute salpingitis group was so large that it precluded reliance on these factors to differentiate the individual patient with acute salpingitis from the patient with the normal pelvis. Only 30% of patients with visually confirmed acute salpingitis had a documented fever. Only 20% of the patients who were confirmed visually to have acute salpingitis had a combination of the classically described signs and symptoms of pelvic pain, purulent cervical discharge, cervical motion tenderness, adnexal tenderness, fever, leukocytosis, and elevated ESR. Thus, it has become apparent that no single symptom or sign can distinguish the group with PID. In an interesting investigation, Wolner-Hanssen et al. (320) reported on the laparoscopic findings in 104 women who presented with pelvic pain, adnexal tenderness, and *C. trachomatis* isolation from the cervix. Despite such a triad of findings, 28 (27%) of the women had no laparoscopic evidence of acute salpingitis. Although the women documented to have salpingitis were significantly more likely to have had pelvic pain of longer duration, irregular bleeding, and an elevated ESR, none of these findings were of a high predictive value. Moreover, there was no statistical difference noted between the women with and those without salpingitis for the presence of a temperature more than or equal to 38°C or a WBC count of more than 10,000 WBC/mm^3.

Clinical Findings	Acute PID (N = 59) (%)	Normal Pelvis on Laparoscopy (N = 184) (%)	p
Adnexal tenderness	573 (97.0)	160 (87.0)	0.05
Increased ESR	473 (76.0)	97 (53.0)	0.001
Abnormal vaginal discharge	394 (63.7)	74 (40.2)	0.001
Fever	205 (33.0)	26 (14.0)	0.001

PID, pelvic inflammatory disease; ESR, erythrocyte sedimentation rate.
Source: From Jacobson L, Westrom L. Objectivized diagnosis of acute pelvic inflammatory disease. Am J Obstet Gynecol 1969;105:1088, with permission.

TABLE 14.14. OBJECTIVE FINDINGS ON ADMISSION IN PATIENTS WITH ACUTE PID

Symptoms	Acute Pelvic Inflammatory Disease (N = 622) (%)	Pelvis Normal on Laparoscopy (N = 184) (%)	p
Lower abdominal pain	585 (94.0)	173 (94.0)	NS
Increased vaginal discharge	340 (54.6)	104 (56.5)	NS
History of fever or chills	257 (41.0)	36 (19.6)	0.001
Irregular bleeding	221 (35.5)	79 (42.9)	NS
Urinary symptoms	116 (18.6)	37 (20.1)	NS
Gastrointestinal symptoms	64 (10.3)	17 (9.2)	NS

Source: From Jacobson L, Westrom L. Objectivized diagnosis of acute pelvic inflammatory disease. Am J Obstet Gynecol 1969;105:1088, with permission.

TABLE 14.13. FREQUENCY OF SYMPTOMS AMONG WOMEN WITH ACUTE PELVIC INFLAMMATORY DISEASE

Westrom (321) further analyzed the prevalence of clinical and laboratory findings in women with laparoscopic confirmation of PID according to etiologic agent (Table 14.15). Whereas gonococcal PID was significantly associated with a symptom duration of 3 or less days, chlamydial PID was significantly associated with symptoms lasting more than 7 days. A temperature of more than or equal to 38°C was more commonly detected with *N. gonorrhoeae,* as were palpable adnexal masses. On the other hand, *C. trachomatis* was more frequently associated with abnormal uterine bleeding and an elevated ESR.

	N. gonorrhoeae (%) (n = 19)	C. trachomatis (%) (n = 68)	Non-N. gonorrhoeae, Non-C. trachomatis (%) (n = 64)
Duration of pelvic pain			
≤3 d	32	15	38
>10 d	21	41	27
Temperature ≥38°C	52	22	30
Palpable adnexal mass	52	25	20
Erythrocyte sedimentation rate ≥30 mm/hr	32	65	19
Irregular bleeding	25	40	30

Source: From Eschenbach DA, Wölner-Hanssen P, Hawes SE, et al. Acute pelvic inflammatory disease: association of clinical and laboratory findings with laparoscopic findings. Obstet Gynecol 1993;81: 1184–192, with permission.

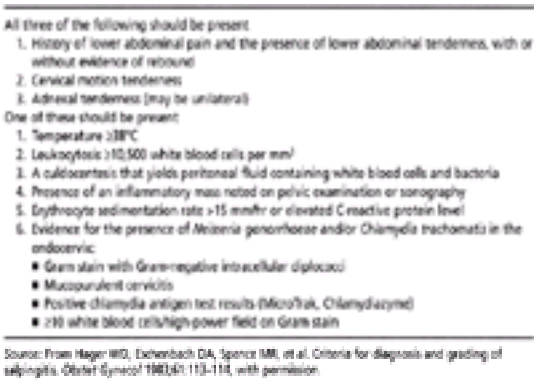
TABLE 14.15. PREVALENCE OF CLINICAL AND LABORATORY FINDINGS IN WOMEN WITH LAPAROSCOPICALLY CONFIRMED PELVIC INFLAMMATORY DISEASE

A wet mount of vaginal secretions containing increased numbers of leukocytes is a very useful but often overlooked sign of acute PID (4,102,115,321,322). Mucopurulent cervicitis is associated with chlamydial and gonococcal infection of the cervix and may be a better indicator of upper genital tract infection (4). However, in populations with a high prevalence of *C. trachomatis* or *N. gonorrhoeae,* mucopurulent cervicitis has a low positive predictive value for acute PID (4). Most importantly, the absence of mucopurulent cervicitis or inflammatory cells in the wet mount of genital secretions carries an excellent negative predictive value for excluding PID. None of the patients in Westrom's Swedish cohort with laparoscopically confirmed PID had an entirely normal vaginal wet mount and clear cervical secretions (4,115,321). Recently, Peipert et al. (322) confirmed the usefulness of the wet mount. These authors reported that a vaginal wet mount containing three or more WBCs per high-power field was more sensitive (87%) than the ESR, CRP level, or peripheral WBC count in patients with symptomatic PID documented by endometrial biopsy or laparoscopy.

In summary, laparoscopic studies have shown that (a) the clinical diagnosis of acute PID is often inaccurate, (b) acute PID is frequently found in patients undergoing laparoscopy for other causes of acute pelvic pain, (c) the laparoscope is a safe way to make the visual diagnosis, and (d) laparoscopy is an excellent means of obtaining cultures directly from the tube, cul-de-sac, and peritoneal cavity. Sellors et al. (307) and Kenney and Greenhalf (323) questioned the accuracy of laparoscopy for the diagnosis of PID. Based on fimbrial biopsy evidence of salpingitis, laparoscopy visualization had a sensitivity of only 50% and a specificity of 85% in a group of primary care patients evaluated by Sellors et al. (307).

Although laparoscopy is currently the accepted “gold standard” for the diagnosis of acute PID, it is logistically and economically impractical for all patients suspected of having acute PID to undergo diagnostic laparoscopy in the United States. For these reasons, an attempt has been made to standardize the diagnosis of acute PID based on clinical grounds. The criteria presented in Table 14.16 have been proposed for making the diagnosis of salpingitis based on clinical grounds. It is suggested that all patients have the initial three findings. Rebound tenderness is not required because

rebound may not be present early in the disease process until there is purulent exudate spilled into the peritoneal cavity and pelvic peritonitis develops. However, because these findings are all subjective and based on pain and tenderness, at least one of the six additional findings, which suggest the presence of acute inflammation, should also be present. To date, these clinical criteria have not been tested clinically. Moreover, they are not intended to be an absolute standard for confirmation of the diagnosis of PID but are an attempt to facilitate inclusion of patients with milder PID that does not fulfill the rigid older criteria.



All three of the following should be present
1. History of lower abdominal pain and the presence of lower abdominal tenderness, with or without evidence of rebound
2. Cervical motion tenderness
3. Adnexal tenderness (may be unilateral)

One of these should be present:
1. Temperature >38°C
2. Leukocytosis >10,500 white blood cells per mm³
3. A culdocentesis that yields peritoneal fluid containing white blood cells and bacteria
4. Presence of an inflammatory mass noted on pelvic examination or sonography
5. Erythrocyte sedimentation rate >15 mm/hr or elevated C-reactive protein level
6. Evidence for the presence of *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* in the endocervix:
   - Gram stain with Gram-negative intracellular diplococci
   - Mucopurulent cervicitis
   - Positive chlamydia antigen test results (MicroTrak, Chlamydiazyme)
   - ≥10 white blood cells/high-power field on Gram stain

Source: From Hager WD, Eschenbach DA, Spence MR, et al. Criteria for diagnosis and grading of salpingitis. Obstet Gynecol 1983;61:113–114, with permission.

TABLE 14.16. CRITERIA FOR THE DIAGNOSIS OF ACUTE SALPINGITIS

Kahn et al. (309) recently assessed the accuracy of existing diagnostic indicators for PID. These authors identified 12 studies in which PID had been diagnosed by laparoscopy or narrow clinical rules that could be included in the analysis. The diagnostic findings were divided into four categories: historical (symptoms), clinical examination (signs), laboratory, and combinations of the first three. Symptoms (duration of pain, irregular menses, fever or chills, sexual contact with known *N. gonorrhoeae* carriers, IUD use, urinary symptoms, gastrointestinal symptoms, age, and marital status) were usually not statistically significant predictors of PID, and when they were, they had low sensitivity and high specificity (309). Clinical findings (abnormal vaginal discharge, purulent vaginal discharge, palpable mass, temperature of more than 38°C) were slightly more sensitive but still suffered from relatively low sensitivity despite high specificity (309). On the other hand, several laboratory tests were shown to be of consistent value in the diagnosis of PID, with both high sensitivity and high specificity (309). The CRP level was significantly elevated when it was assessed and showed a sensitivity of 74% to 93% and a specificity of 50% to 90%. Elevated ESRs demonstrated a sensitivity range of 64% to 81% and a specificity of 43% to 69% using more than or equal to 20 mm per hour or more than or equal to 15 mm per hour. With an ESR of more than 25 mm per hour, the sensitivity was 55% and the specificity was 84%.

Endometrial biopsy demonstrating endometrial inflammation had good sensitivity and specificity rates (309) and has been suggested as a less invasive alternative to laparoscopy for verifying a clinical diagnosis of acute PID (Table 14.17). Paavonen et al. (99,325) reported a 90% correlation for histologic endometritis and laparoscopically confirmed salpingitis. Similarly, Wasserheit et al. (44) reported that

plasma cell endometritis was present in 14 (70%) of 20 women with laparoscopically confirmed salpingitis, compared with 1 (7.7%) of 13 women without salpingitis. According to Kiviat et al. (142), the histologic features of endometritis associated with laparoscopy-proven salpingitis include plasma cells in the endometrial stroma, polymorphonuclear leukocytes in endometrial surface epithelium, intraluminal polymorphonucleocytes, dense subepithelial stromal lymphocytic infiltration, and germinal centers containing transformed lymphocytes. The combination of more than one plasma cell per 120× field in endometrial stroma and more than five polymorphonuclear leukocytes per 400× field gave the best prediction for laparoscopically confirmed PID, with a sensitivity of 92% and a specificity of 87% (142). In summary, the presence of endometritis on biopsy has both a good sensitivity (70% to 89%) and a good specificity (67% to 89%) (99,140,325). Unfortunately, results are not available for 2 to 3 days; thus, its clinical applicability is limited.

Author	PID Diagnostic Criteria	Endometritis Diagnostic Criteria	Sensitivity	Specificity	Positive Predictive Value
Paavonen et al., 1985 [99]	Laparoscopy	Plasma cells	89%	67%	94%
Wasserheit et al., 1986 [64]	Laparoscopy	Plasma cells	70%	100%	100%
Kiviat et al., 1990 [142]	Laparoscopy	Neutrophils in superficial layer Plasma cells	78%	95%	91%
Sellors, 1988 [325]	Laparoscopy Fimbrial biopsy	Plasma cells Lymphoid aggregates Polymorphonuclear leukocytes	33%	98%	91%

TABLE 14.17. ENDOMETRIAL BIOPSY FOR THE DIAGNOSIS OF PELVIC INFLAMMATORY DISEASE (PID)

Several authors suggest that ultrasound examination is useful in the diagnosis of PID, particularly when pyosalpinx or TOA complicates the presentation (326,327,328,329 and 330). Spirtos (328) reported that transabdominal ultrasound predicted PID in 94% of women with confirmed severe PID, 80% of those with moderate cases, and 64% of those with mild cases. Cacciatore et al. (329) recently reported that transvaginal sonography can facilitate and improve the ultrasound diagnosis of acute PID. Using plasma cell endometritis as the criterion for PID, these authors reported that a sonogram suggestive of PID (i.e., thickened fluid-filled tube with or without free pelvic fluid) had a sensitivity of 85% and a specificity of 100% for the diagnosis of histologic endometritis (329). More recently, Boardman et al. (330) confirmed that although endovaginal sonography had an excellent specificity (97%) for identifying fallopian tubes (with or without intraluminal fluid), its clinical use is limited by a poor sensitivity (32%). The role of sonography as a noninvasive diagnostic test for PID remains to be further elucidated. Not only does endovaginal sonography require further study, but studies using color flow Doppler technology and three-dimensional ultrasound would be useful.

Additional laboratory tests that have been studied as predictors of acute PID include

antichymotrypsin (321), ovarian cancer tumor marker cancer antigen 125 test (CA125) (4,332), tumor-associated trypsin inhibitor (309), and specific genital isoamylases (4). These remain investigational and have not been shown to have a good positive predictive value.

Procedures such as sonography and culdocentesis may not be readily available to physicians in general practice. Thus, the clinician may still have to base the diagnosis of acute PID on observation for the classical signs and careful history taking. Kahn et al. (309) proposed a new diagnostic model for PID based on four objectives: (a) choose diagnostic criteria based on careful understanding of scientific literature, (b) emphasize diagnostic sensitivity for mild disease and accurate diagnosis (specificity) for severe disease, (c) standardize the selection and interpretation of diagnostic indicators, and (d) clarify the process of collecting information, starting with initial overall assessment, moving to simple input (history, examination, simple laboratory tests) and progressing as necessary to more expensive and invasive assessment (e.g., endometrial biopsy, ultrasonography, and laparoscopy). In essence, this model (Fig. 14.6) proposes a diagnostic approach that emphasizes diagnostic sensitivity when clinical presentation is mild, and more thorough evaluation when the patient is more severely sick.

FIGURE 14.6. Diagnostic model for pelvic inflammatory disease.

In a similar vein, the CDC subsequently recommended a “low threshold for diagnosis” of PID because of concern for the potential damage to the reproductive health of women (9). The CDC recommends that in mild cases, treatment of PID should be instituted on the basis of the minimum criteria, as listed in Table 14.18 (9). All three of the criteria (lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness) should be present. However, Peipert et al. (334) reported that compared with laparoscopic confirmation of salpingitis, the minimum criteria proposed by the CDC had a poor sensitivity (51%). When patients present with more severe clinical findings, more elaborate diagnostic evaluation is suggested to preclude incorrect diagnosis or unnecessary morbidity. These additional criteria (Table 14.18) include an oral temperature of more than 38.3°C (101°F), abnormal cervical or vaginal discharge, elevated ESR, elevated CRP, and laboratory documentation of cervical infection of *N. gonorrhoeae* or *C. trachomatis.* The routine criteria are those that are simple and relatively inexpensive. Although more specific,

the elaborate criteria are more costly and often invasive. Short of invasive diagnostic tests, clinical symptoms and signs and laboratory tests are poor predictors of acute PID, as noted in Table 14.19, which demonstrates the wide range and specificity associated with these factors. In the 1998 guidelines for the treatment of PID, the CDC listed three definite criteria for diagnosing PID: (a) histopathologic evidence of endometritis on endometrial biopsy, (b) transvaginal ultrasonography or other imaging techniques showing thickened fluid-filled tubes or tuboovarian complex, and (c) laparoscopic abnormalities consistent with PID (110).

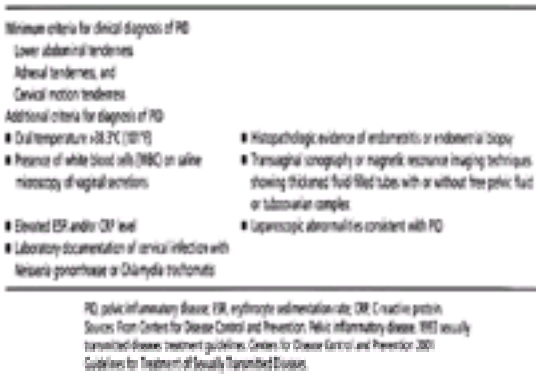

Minimum criteria for clinical diagnosis of PID
Lower abdominal tenderness
Adnexal tenderness, and
Cervical motion tenderness
Additional criteria for diagnosis of PID
• Oral temperature >38.3°C (101°F)
• Presence of white blood cells (WBC) on saline microscopy of vaginal secretions
• Elevated ESR and/or CRP level
• Laboratory documentation of cervical infection with Neisseria gonorrhoeae or Chlamydia trachomatis
• Histopathologic evidence of endometritis on endometrial biopsy
• Transvaginal sonography or magnetic resonance imaging techniques showing thickened fluid-filled tubes with or without free pelvic fluid or tuboovarian complex
• Laparoscopic abnormalities consistent with PID
PID, pelvic inflammatory disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
Source: From Centers for Disease Control and Prevention. Pelvic inflammatory disease. 1993 sexually transmitted diseases treatment guidelines. Centers for Disease Control and Prevention 2001 Guidelines for Treatment of Sexually Transmitted Diseases.

TABLE 14.18. CRITERIA FOR CLINICAL DIAGNOSIS OF PID AS RECOMMENDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION

Additional Criteria	Sensitivity	Specificity
Oral temperature ≥38.3°C	24–40%	79–86%
Abnormal cervicalvaginal discharge	26–81%	42–85%
Elevated ESR	64–81%	25–69%
Elevated CRP	74–62%	50–90%
Evidence of cervical infection with Neisseria gonorrhoeae or Chlamydia trachomatis	77%	77%
Histopathologic evidence of endometritis	70–89%	67–90%
Tuboovarian abscess on ultrasound		
Laparoscopic evidence of pelvic inflammatory disease	100%	61%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
Source: From Centers for Disease Control and Prevention. Pelvic inflammatory disease. 1993 sexually transmitted diseases treatment guidelines. MMWR Morb Mortal Wkly Rep 1993;42:75.

TABLE 14.19. SENSITIVITY AND SPECIFICITY OF ADDITIONAL CRITERIA FOR DIAGNOSIS OF PELVIC INFLAMMATORY DISEASE

Not only are clinical symptoms and signs and laboratory tests poor predictors of acute PID, but they do not accurately predict the extent of fallopian tube disease or damage (318,322). Eschenbach et al. (318) reported that patients with tubal occlusion or moderate to severe tubal adhesions were equally distributed among the patients presenting with mild to moderate clinically apparent PID and those with

severe clinical symptoms and signs.

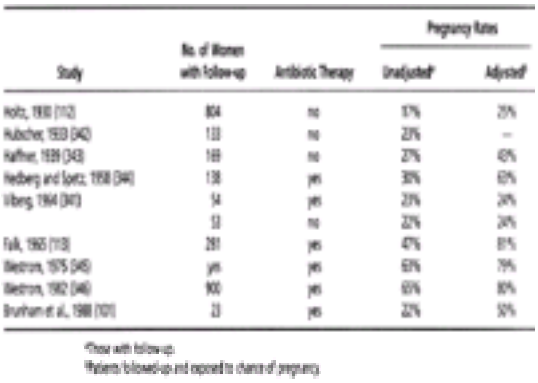
The seroprevalence of HIV among women with PID is higher than that in women without PID (334). Concern has risen that HIV infection might effect the clinical presentation, microbiology, or the course of acute PID. The effect of HIV on PID is discussed in detail in Chapter 10 (Acquired Immunodeficiency Syndrome [AIDS]). Most studies have demonstrated that HIV-infected women with PID present with lower mean WBC counts and higher temperatures (334). TOAs (335) and surgical intervention (333) are reported more commonly but not consistently (336).

In general, the diagnosis of TOAs has been based on clinical findings, such as pelvic examination revealing a tender pelvic mass, in association with the signs and symptoms of PID. The diagnosis of TOAs based on physical examination has been questioned because of the difficulty in evaluating the bimanual examination in women with acute pelvic peritonitis. Differentiating a TOA from acute PID with bowel adhered to the adnexa is difficult. Recently, sonography and computed tomographic (CT) scanning have been suggested as methods to increase diagnostic accuracy (257). Sonography may prove to be an accurate replacement for documenting the presence of an abscess by surgically draining the purulent material. However, the routine use of sonography in patients with acute salpingitis does not seem indicated. Rather, if the patient is not able to be adequately examined because of tenderness and pain to exclude an adnexal mass, or if there is a lack of response to antimicrobial therapy in the initial 48 to 72 hours of therapy, sonography may be indicated to evaluate the possibility of an inflammatory mass being present.

TREATMENT

It is important to recognize that the therapeutic goal in the management of acute PID is to prevent infertility, ectopic pregnancy, and the chronic residua of infection. Before the advent of antibiotics, many cases of acute salpingitis managed by conservative supportive therapy resolved spontaneously and without sequelae (112,337,338). Curtis (337,338) stated that 85% of patients with acute salpingitis improved without surgery, whereas 15% had prolonged or progressive symptoms that led to surgical intervention. In a review of 1,262 patients, Holtz (112) noted a 9% incidence of persistent severe symptoms, a 6% incidence of pyrexia present for more than 2 months, and a 1.3% incidence of mortality. Studies from Scandinavia in the late 1950s and early 1960s suggested that the advent of antibiotics had improved the prognosis for acute PID: Mortality had been eliminated; the frequency of ruptured pelvic abscesses and persistent masses requiring surgery had decreased; and the subsequent fertility rate had improved (113,339,340). In the preantibiotic era, Holtz (112) reported a 22.8% pregnancy rate in patients with gonococcal salpingitis. These early studies noted that the use of antibiotics for the treatment of gonococcal salpingitis resulted in crude pregnancy rates of 39% to 51% (112,113). If patients with gonococcal salpingitis who are voluntarily infertile or in whom surgical intervention precluded conception are excluded, corrected pregnancy rates of 67% to 84% are reported (112,113). Antibiotic treatment in cases of nongonococcal salpingitis resulted in crude pregnancy rates of 25% to 44% and corrected pregnancy rates of 60% to 81% (112,340,341). Westrom and Berger (265) recently summarized the prospective studies on fertility after PID, comparing studies before and after the introduction of antimicrobial treatment of PID. These studies (Table 14.20) demonstrate that fertility has generally improved with the introduction of antimicrobial therapy. In these studies, the mean pregnancy rate in women attempting pregnancy

was 27.9% in the preantibiotic era, compared with 73.1% after the introduction of antibiotic treatment. For the preantibiotic group, the pregnancy rates ranged from 24% to 43%, whereas after antibiotic therapy, the range was 24% to 81%.



Study	No. of Women with Follow-up	Antibiotic Therapy	Pregnancy Rates	
			Unadjusted[a]	Adjusted[b]
Holtz, 1980 [112]	804	no	51%	75%
Hulbucher, 1953 [342]	133	no	23%	–
Kaliher, 1939 [343]	169	no	27%	43%
Hedberg and Sparks, 1958 [344]	138	yes	30%	63%
Viberg, 1964 [341]	54	yes	23%	24%
	53	no	22%	24%
Falk, 1965 [113]	261	yes	47%	81%
Westrom, 1975 [345]	yes	yes	65%	79%
Westrom, 1982 [346]	900	yes	65%	80%
Brunham et al., 1988 [101]	23	yes	22%	50%

[a]Those with follow-up.
[b]Patients followed-up and exposed to chance of pregnancy.

TABLE 14.20. FOLLOW-UP STUDIES OF FERTILITY IN WOMEN WITH PELVIC INFLAMMATORY DISEASE IN THE PREANTIBIOTIC AND POSTANTIBIOTIC ERA

Although on the surface, it appears that antimicrobial therapy has improved the prognosis for fertility significantly, the results are far from satisfactory. The higher pregnancy rates after antibiotic treatment are corrected rates that have excluded patients for whom the infection resulted in surgical intervention that prevented fertility. Exclusion of such patients may preclude a fair assessment, because the true prognosis for fertility rates was similar in the group treated with antibiotics and in the control group treated with bed rest and supportive therapy only (341).

Early diagnosis and treatment are crucial to the preservation of fertility. Several investigations have shown that the effectiveness of therapy in preventing infertility depends on the interval between the onset of symptoms and the institution of treatment (113,339,341). These follow-up investigations, which used hysterosalpingogram or laparoscopy, have documented that in women treated early in the course of acute salpingitis, tubal patency remained unimpaired in a significant number of women. Viberg (341) reported that none of the patients treated within 2 days of the onset of symptoms were involuntarily infertile, and all had patent fallopian tubes on hysterosalpingogram. On the other hand, if treatment had been instituted on day 7 or later, only 70% of patients were shown to have tubal patency. Hillis et al. (83) reported that women treated after 3 or more days of symptoms had a significantly greater infertility rate than that of those treated within less than 3 days of symptom onset (19.7% vs. 8.3%). Interestingly, animal model studies of acute chlamydial PID have confirmed that a short window, within 5 to 6 days of disease onset, exists within which good fertility outcome can be accomplished by antibiotic treatment (170). These findings again stress the importance of not relying on the strict criteria for the diagnosis of acute salpingitis that have existed in the past, as well as of the necessity to institute early treatment based on a more flexible and realistic approach to the diagnosis.

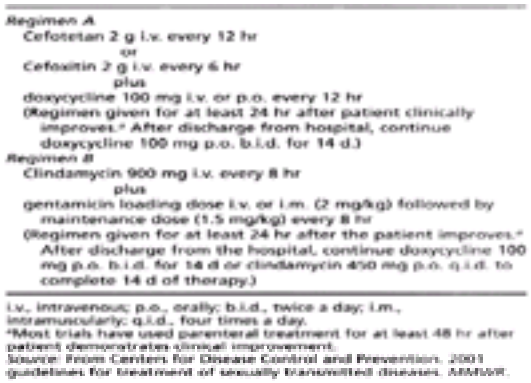
The failure of antibiotics to prevent the sequelae of acute salpingitis may reflect the emphasis on gonorrhea as an etiologic agent and the lack of antimicrobial regimens that provide coverage for the polymicrobic etiology of acute salpingitis, including chlamydia and anaerobic bacteria. If antibiotic therapy is to be effective and prevent the sequelae of salpingitis, it must be instituted early in the disease process. In addition, an antibiotic regimen that considers the polymicrobial nature of the etiology of acute salpingitis must be used. The major pathogens include *C. trachomatis, N. gonorrhoeae, Prevotella* sp (formerly *Bacteroides* sp), *Peptostreptococcus* sp, and aerobic bacteria such as *G. vaginalis, E. coli,* and facultative streptococci. Whether it is necessary to cover all these organisms is not proven. Brunham et al. (101) noted that chlamydial infection and anaerobic infection with abscess formation were associated with post-PID infertility. Recently, Walker et al. (260) reviewed the role of anaerobes in acute PID and their implication for the treatment of PID. These authors noted the concern that tissue damage may continue to occur when anaerobes are suboptimally treated, and that therefore many experts advise use of regimens that include comprehensive anaerobic coverage. Westrom et al. (347) noted that in a group of 604 laparoscopically confirmed cases of first-episode acute PID, the infertility rate on long-term follow-up ranged from 10% to 13% regardless of the type of antibiotic regimen. However, none of the regimens used provided adequate coverage for all three of the major etiologic groups: *N. gonorrhoeae, C. trachomatis,* and anaerobic-aerobic bacteria.

In the past, controversy existed over the issue of outpatient treatment with oral antibiotics versus inpatient treatment with parenteral antibiotics in patients with acute PID. There are no data available to evaluate the need for hospital versus ambulatory management of acute PID before the era of managed care. For economic and logistic reasons, only 20% to 25% of cases were hospitalized in the United States; most remained outpatients during treatment. In the age of managed care, hospitalization rates for acute PID have decreased and currently only an estimated 15% of cases are treated as inpatients. In addition, rather than comparing ambulatory with hospitalized treatment, the issue revolves around oral versus parenteral (home ambulatory treatment or hospitalized). The CDC published recommended treatment schedules for acute PID (110) (Table 14.21 and Table 14.22). The current recommended treatment regimens are based on the premise that it is appropriate to cover all the major etiologic agents involved in acute salpingitis, including *N. gonorrhoeae, C. trachomatis,* anaerobes including peptostreptococci and *Prevotella* organisms, Gram-negative enterics such as *E. coli, G. vaginalis,* and anaerobic streptococci.

Regimen A
Ofloxacin 400 mg p.o. b.i.d. for 14 d or Levofloxacin 500 mg orally once daily
plus
metronidazole 500 mg p.o. b.i.d. for 14 d
Regimen B
Ceftriaxone 250 mg i.m. once
or
Cefoxitin 2 g i.m. plus probenecid 1 g p.o. in a single dose concurrently
or
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
plus
Doxycycline 100 mg p.o. b.i.d. for 14 d with or without metronidabole 500 mg orally bid × 14d

p.o., orally; b.i.d., twice a day; i.m., intramuscularly.
Source: From Centers for Disease Control and Prevention. 2001 guidelines for treatment of sexually transmitted diseases. MMWR.

TABLE 14.21. CENTERS FOR DISEASE CONTROL AND PREVENTION–RECOMMENDED TREATMENT SCHEDULES FOR ORAL TREATMENT OF ACUTE PELVIC INFLAMMATORY DISEASE—2001



Regimen A
Cefotetan 2 g i.v. every 12 hr
or
Cefoxitin 2 g i.v. every 6 hr
plus
doxycycline 100 mg i.v. or p.o. every 12 hr
(Regimen given for at least 24 hr after patient clinically improves.[a] After discharge from hospital, continue doxycycline 100 mg p.o. b.i.d. for 14 d.)
Regimen B
Clindamycin 900 mg i.v. every 8 hr
plus
gentamicin loading dose i.v. or i.m. (2 mg/kg) followed by maintenance dose (1.5 mg/kg) every 8 hr
(Regimen given for at least 24 hr after the patient improves.[a] After discharge from the hospital, continue doxycycline 100 mg p.o. b.i.d. for 14 d *or* clindamycin 450 mg p.o. q.i.d. to complete 14 d of therapy.)

i.v., intravenous; p.o., orally; b.i.d., twice a day; i.m., intramuscularly; q.i.d., four times a day.
[a]Most trials have used parenteral treatment for at least 48 hr after patient demonstrates clinical improvement.
Source: From Centers for Disease Control and Prevention. 2001 guidelines for treatment of sexually transmitted diseases. MMWR.

TABLE 14.22. CENTERS FOR DISEASE CONTROL AND PREVENTION–RECOMMENDED TREATMENT SCHEDULES FOR PARENTERAL (INPATIENT OR OUTPATIENT) TREATMENT OF ACUTE PELVIC INFLAMMATORY DISEASE—2001

Secondly, the CDC suggests that among currently Food and Drug Administration–approved antibiotics, single-agent therapy is not appropriate for PID. No prospective data exist to address the issue of the clinical efficacy of oral (outpatient) versus parenteral (inpatient) therapy of acute PID. The answer must await large-scale prospective studies that include sufficiently long duration of posttreatment follow-up to allow for an assessment of the impact on fertility and ectopic pregnancy, as well as the need for surgical intervention. Such is currently underway and the results are eagerly awaited.

The clinician who diagnoses acute PID is faced with the question of hospitalization, and in the case of ambulatory treatment, oral versus parenteral therapy. There is no satisfactory solution to this dilemma, and the controversy between ambulatory and hospital or oral versus parenteral management still wages. Indications for hospitalization of patients with acute PID have been suggested and are listed in Table 14.23. We feel it is important to admit patients who have not responded promptly to ambulatory oral therapy; it is crucial to reevaluate patients within 48 hours to determine the effectiveness of oral therapy, and if no response has been obtained, admission should be promptly instituted with parenteral antibiotics to hopefully prevent the sequelae of salpingitis. Patients with suspected or diagnosed TOAs should be hospitalized to receive parenteral therapy. We recommend that women wearing IUDs should be treated on an inpatient basis, because of the high coexistent rate of adnexal inflammatory masses. Previously, it was suggested that all adolescents with salpingitis should be hospitalized because of the high

noncompliance rate among the adolescent population, particularly with the use of multiple doses in therapy. The current recommendation for hospitalization of patients unable to follow an outpatient oral regimen encompasses the previous focus on adolescents.

1. Surgical emergencies such as appendicitis cannot be excluded
2. Patient is pregnant
3. Patient does not respond clinically to oral antimicrobial therapy
4. Patient unable to follow or tolerate outpatient oral regimen
5. Patient has severe illness, nausea and vomiting, or high fever
6. Patient has tuboovarian abscess
7. Patient is immunodeficient (i.e., human immunodeficiency virus infection with low CD4 cell counts, immunosuppressive therapy)

Source: From Centers for Disease Control and Prevention. 2001 guidelines for treatment of sexually transmitted diseases. MMWR.

TABLE 14.23. CRITERIA FOR HOSPITALIZATION OF PATIENTS WITH ACUTE PELVIC INFLAMMATORY DISEASE

The major emphasis has been to use combinations of agents to provide empiric broad-spectrum coverage of the multitude of microorganisms involved in the polymicrobial etiology of acute PID. This is readily accomplished with the parenteral regimens. The cefotetan or cefoxitin plus doxycycline regimen appears to provide coverage against all the major pathogen groups. Doxycycline is active against *C. trachomatis.* The cefotetan or cefoxitin regimen covers *N. gonorrhoeae* (including most penicillinase-producing strains), Gram-positive aerobes, Gram-negative aerobes, and penicillin-sensitive and non–penicillin-sensitive anaerobes. The use of cefotetan has the advantage of twice-daily dosing. Sweet et al. (45) compared cefoxitin plus doxycycline with cefotetan plus doxycycline for the treatment of acute PID and noted equal and excellent initial clinical efficacy with both regimens. Because of pain associated with infusion, it is suggested that doxycycline be administered orally when possible, even in hospitalized patients (110). Other second- or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone) have been less well studied and are less active against anaerobic bacteria (110). Although the clindamycin plus gentamicin combination provides excellent activity against anaerobes (clindamycin), Gram-negative aerobes (gentamicin), and Gram-positive aerobes (clindamycin), it does not provide optimal activity against *C. trachomatis* and *N. gonorrhoeae. In vitro* studies have demonstrated that clindamycin is effective against approximately 90% of *C. trachomatis* strains (348); its efficacy in clinical cases of chlamydial salpingitis has recently been demonstrated. Wasserheit et al. (44) reported that clindamycin effectively eradicated *C. trachomatis* in 100% of cases of chlamydial salpingitis. Sweet et al. (349) confirmed the clinical efficacy of clindamycin against *C. trachomatis* in patients with acute PID. Although neither clindamycin nor aminoglycosides are the agent of choice against *N. gonorrhoeae,* they are both effective against non–penicillinase-producing strains (233). Alternative parenteral regimens for the treatment of acute PID have been infrequently studied. The CDC suggests that at least three alternative parenteral

regimens, which have been investigated in at least one clinical trial, might be considered (110). These are (a) 400 mg of ofloxacin intravenously every 12 hours plus 500 mg of metronidazole intravenously every 8 hours; (b) 3 g of ampicillin-sulbactam intravenously every 6 hours plus 100 mg of doxycycline intravenously or orally every 12 hours; or (c) 200 mg of ciprofloxacin intravenously every 12 hours plus 100 mg of doxycycline intravenously or orally every 12 hours plus 500 mg of metronidazole intravenously every 8 hours. Metronidazole is added to quinolone regimens to provide anaerobic coverage (350). Because ciprofloxacin has poor coverage against *C. trachomatis,* doxycycline is added to provide antichlamydial activity.

The 1998 CDC guidelines for oral treatment include a combination of ofloxacin plus metronidazole (110). In this regimen, ofloxacin covers *N. gonorrhoeae* and *C. trachomatis* while metronidazole provides coverage for anaerobes. Ofloxacin is active against Gram-negative enterics. However, aerobic streptococci are not well covered. In regimen B, many authorities add metronidazole to the cephalosporin plus doxycycline regimen to provide improved coverage against anaerobic bacteria. In addition, the metronidazole will effectively treat BV, which is frequently associated with PID (110). Although not recommended by the CDC, azithromycin (1 g orally as a single dose) is a popular alternative to the use of doxycycline in the oral regimen. This is particularly true when compliance is an issue. However, the single 1-g dose should be repeated on day 8 to provide 14 days of therapy. Moreover, no prospective data have been published assessing the efficacy of azithromycin in treating acute PID.

Unfortunately, few microbiologically controlled prospective studies comparing the various antibiotic regimens have been reported. Walker et al. (139) performed a metaanalysis of antimicrobial regimen efficacy for the treatment of acute PID (Table 14.25). They identified 34 treatment studies published between 1966 and 1992, of which 21 met their criteria for inclusion: appropriate system for making diagnosis of PID, standardized assessment of clinical outcome, and entry and follow-up evaluation for cervical infection with *N. gonorrhoeae* and *C. trachomatis,* The pooled clinical cure rates ranged from 75% to 94% and the pooled microbiologic cure rates ranged from 71% to 100% (Table 14.24 and Table 14.25). With the exception of the metronidazole plus doxycycline regimen, these antimicrobial regimens appear to have excellent short-term clinical and microbiologic efficacy. The antimicrobial spectrum of activity and costs of these regimens are provided in Table 14.26. In the United States, no data are available to assess the effect of therapy on long-term outcomes such as infertility and ectopic pregnancies. More such studies are urgently needed to determine whether all potential pathogens must be covered by antimicrobial therapy. No well-controlled study has yet compared short- and long-term outcomes of oral (outpatient) versus parenteral (inpatient) regimens. Such a large collaborative study is currently being completed (PEACH study; R. Ness, *personal communication,* 2001). To ensure the best possible prognosis for fertility and to prevent other serious long-term sequelae, it is our belief that vigorous parenteral treatment, coupled with careful outpatient follow-up, is essential.

Drug Regimen	No. of Studies	No. of Patients	Clinical Cure Rate	Microbiologic Cure Rate[a]
Inpatient				
Soluble specific substance	10	372	52%	57%
Cefoxitin-doxycycline	7	338	95%	98%
Cefotetan-doxycycline	2	86	94%	100%
Ciprofloxacin	4	90	94%	96%[b]
Metronidazole-doxycycline	2	36	75%	71%
Outpatient				
Cefoxitin-doxycycline	2	59	95%	91%

[a]Microbiologic cure based on eradication of Neisseria gonorrhoeae and Chlamydia trachomatis.
[b]High rate of persistent anaerobic bacteria noted (3/47).

TABLE 14.24. REPORTED POOLED CURE RATES IN TREATMENT OF ACUTE PELVIC INFLAMMATORY DISEASE FOR ANTIBIOTIC REGIMENS WITH MORE THAN ONE STUDY INCLUDED IN THE METAANALYSIS BY WALKER ET AL. (139)

Drug Regimen	No. of Patients	Clinical Cure Rate	Microbiologic Cure Rate[a]
Inpatient			
Ceftizoxime-tetracycline	18	88%	100%
Cefotaxime-tetracycline	19	84%	100%
Sulbactam-ampicillin-doxycycline	37	95%	100%
Outpatient			
Amoxicillin-clavulanic acid	35	100%	100%
Ofloxacin	37	95%	100%

[a]Based on eradication of Neisseria gonorrhoeae and Chlamydia trachomatis.

TABLE 14.25. REPORTED CURE RATES IN TREATMENT OF ACUTE PELVIC INFLAMMATORY DISEASE FOR ANTIBIOTIC REGIMENS WITH ONLY SINGLE STUDY IN THE METAANALYSIS BY WALKER ET AL. (139)

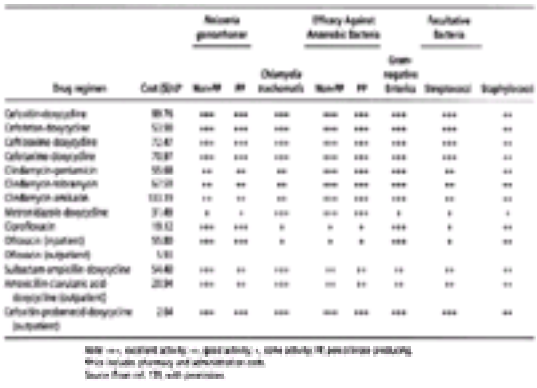


TABLE 14.26. ANTIMICROBIAL ACTIVITY OF REGIMENS INCLUDED IN THE

METAANALYSIS

Appropriate management of acute PID includes examination and treatment of the sexual partners of women with acute PID. These partners should be treated with one of the regimens for uncomplicated gonorrheal and chlamydial infections (i.e., 250 mg of ceftriaxone intramuscularly once a day) followed by doxycycline (100 mg twice a day for 7 days) or azithromycin (1 g orally as a single dose). The importance of treating sexual partners cannot be overstressed. In a surveillance study of gonococcal PID in San Francisco, 13% of male partners screened were asymptomatic urethral carriers of *N. gonorrhoeae* (R. L. Sweet, *unpublished data*). Eschenbach and Holmes (26) reported that 25% of gonococcal PID cases were readmitted to the hospital with a subsequent episode of PID within 10 weeks of initial treatment. Similar, and even higher, rates of asymptomatic chlamydial urethritis in men occur. Women with acute PID return to the same social milieu they were in before treatment, and if the large pool of male partners with asymptomatic *N. gonorrhoeae* and *C. trachomatis* is not treated, they will be exposed to a risk for additional episodes of PID.

TOA is a complication of acute PID and develops when infected material from the fallopian tubes spills into the adjacent ovary and gains access to the ovary. The resulting mass may be unilateral or bilateral and associated with a subacute or chronic disease. It is estimated that palpable adnexal swelling is found in 25% of patients with acute salpingitis, representing acute adnexal inflammation or a TOA. The actual incidence of TOA formation is estimated between 7% and 16% (257,351,352,353,354 and 355). A detailed description of the management of TOAs, only briefly reviewed here, is presented in Chapter 6 (Herpes Simplex Virus Infection). Although treated by radical gynecologic surgery as primary management by some (353), initial treatment of TOA when there is no suspicion of rupture more appropriately includes hospitalization and vigorous medical management with broad-spectrum antibiotic regimens that include coverage of *B. fragilis, N. gonorrhoeae,* anaerobic Gram-positive cocci, and Gram-negative facultative organisms (257,354,355). In patients with suspected TOAs, antibiotic therapy should include a drug that is effective against *B. fragilis,* because of the high prevalence of this anaerobe in association with pelvic abscesses. Both CDC-recommended regimens for hospitalized patients with acute PID contain antimicrobial agents that are effective against *B. fragilis* and penetrate into and are active inside abscesses (356). We believe that conservative medical therapy for TOAs is appropriate in lieu of suspicion of a ruptured TOA, which is a surgical emergency. Ruptured TOAs are reported to occur in 3% to 15% of TOAs (351,354,357). Aggressive surgical intervention with hysterectomy and bilateral salpingo-oophorectomy after spontaneous rupture of a TOA results in a more than 95% recovery rate. Franklin et al. (354), Ginsburg et al. (355), and Landers and Sweet (257) reported that the conservative medical approach to the treatment of TOAs was associated with a 70% response rate. However, if patients do not begin to improve within 48 to 72 hours of institution of antimicrobial therapy, surgical intervention is undertaken, conserving as much of the reproductive system as possible. McNeeley et al. (358) recently noted that adding ampicillin to clindamycin and gentamicin (triple therapy) yielded significantly better results than clindamycin-gentamicin or cefotetan-doxycycline in the treatment of TOAs. It has been proposed that with the use of CT scan and

real-time sonography, percutaneous aspiration and drainage of intraabdominal abscesses is possible (359).

In acute PID, the purulent and inflammatory reaction in the pelvis is often severe, with subsequent adhesions, sterility, and chronic pain. To prevent these sequelae, the concomitant use of steroids has been advocated. However, in a prospective investigation, Falk (113) reported that the use of steroids in the treatment of acute salpingitis produced no difference in the end result as judged by hysterosalpingogram findings, fertility, or the findings at subsequent laparoscopy. Whether the use of a higher dose steroid regimen would be beneficial is speculative. In addition, the role of other antiinflammatory agents (e.g., antiprostaglandins) should be evaluated in investigations as potential aides in preventing the adhesions and scarring that occur after episodes of acute PID.

Reducing the incidence of PID is a goal of the Public Health Service for the year 2000 (360). As noted by Scholes et al. (19), efforts to control PID have been hampered by (a) the various pathogens that cause PID, (b) difficulty in making a diagnosis, (c) frequency of asymptomatic (unrecognized) infections, and (d) lack of adequate surveillance systems.

Schachter (361) emphasized that prevention of PID has two major goals: (a) to prevent the morbidity, lost work, pain, suffering, and medical costs of acute PID and (b) to prevent the long-term sequelae of PID. Because approximately two thirds (up to 75%) of patients with acute PID are associated with *N. gonorrhoeae* or *C. trachomatis,* STD prevention is a major component in any program to prevent PID (359). In view of the frequency of unrecognized PID, both primary and secondary prevention efforts are critical to achieving these goals (361).

Examples of primary prevention of STDs (the etiologic agents of PID) include the following: delayed onset of sexual activity in young women, monogamous sexual relationships, and promotion of condom use. Examples of secondary prevention include the following: preclude IUD use in young nulliparous women, possibly screening for *C. trachomatis* and BV before elective abortion, decreased use of vaginal douching, smoking cessation, and screening programs for *N. gonorrhoeae, C. trachomatis,* and possibly BV.

Hillis and Wasserheit (362) suggested that screening for chlamydia was an important key to preventing PID. This is particularly important in view of the frequency of unrecognized PID associated with *C. trachomatis.* Several reports have provided evidence for the efficacy of screening for chlamydia in preventing PID (19,20,363). Scholes et al. (19) conducted a randomized, controlled trial of selective testing of high-risk women versus usual care of screening only symptomatic women for chlamydia. There was a significant reduction (relative risk, 0.44; 95% CI, 0.20–0.90) in PID among women in the screening group (19). In Sweden, both a reduction in IUD use in young women and a concerted effort to screen for *N. gonorrhoeae* and *C. trachomatis* led to a marked decrease in PID (361). In the United States, implementation of regional, state, and local efforts to prevent chlamydial infection have been followed by precipitous decreases in the prevalence of chlamydial infection (20).

Tertiary prevention involves reducing the risk of the long-term sequelae of PID. This requires early diagnosis and appropriate treatment, as discussed previously. Of

critical importance is diagnosis within 48 hours of symptom onset (83).

SUMMARY

Prevention of the significant medical and economic sequelae of acute PID relies on the institution of appropriate treatment regimens, which are based on the true microbiologic etiology of acute PID and cognizant of the polymicrobic nature of this etiology. The clinician must maintain a high index of suspicion for acute salpingitis so early diagnosis and treatment can be made. We believe that hospitalization and use of parenteral antimicrobial therapy will be of greatest benefit to the patient. This therapy should include combination agents that provide coverage for *N. gonorrhoeae, C. trachomatis,* anaerobes (including *Bacteroides* and anaerobic cocci), Gram-negative aerobic rods, and Gram-positive aerobes (including group B streptococcus). Finally, it is crucial to prevent repeated infections by seeking out the sexual partners of women with acute PID and treating them for STDs. In this way, the recurrent infections, which lead to the poor prognosis for fertility, can be circumvented.

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15

URINARY TRACT INFECTION

As described by Stamm and Hooton (1), urinary tract infections (UTIs) in women can be divided into five categories: (a) young women with acute uncomplicated cystitis; (b) young women with recurrent cystitis; (c) young women with acute uncomplicated pyelonephritis; (d) women of any age with complicated UTI; and (e) asymptomatic bacteriuria (ASB). UTIs are also important causes of nosocomial infections. Distinction between these categories has major implications for antimicrobial treatment (type and duration), pretreatment and posttreatment evaluation, and need for evaluation of the urinary tract.

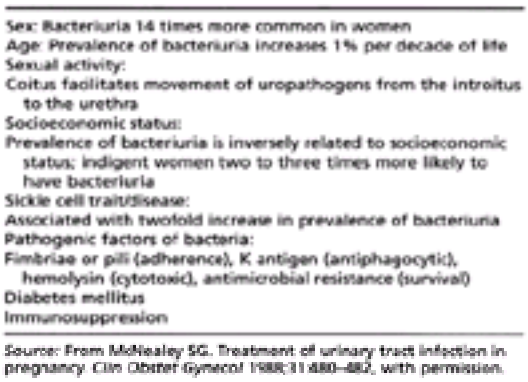
EPIDEMIOLOGY

UTIs are the most common bacterial infections in adult women and UTI in women is a major public health problem, both in terms of morbidity and economic costs. Moreover, UTI is the most common medical complication of pregnancy. UTIs account for an estimated 7 to 8 million office visits (mostly for cystitis) and more than 100,000 hospitalizations (mostly for acute pyelonephritis) annually in the United States (1,2,3 and 4). The annual cost for UTI in ambulatory patients is an estimated $1 billion, with an additional $300 million cost for hospitalized cases of acute pyelonephritis (3). In a large prospective study of young sexually active women in a Health Maintenance Organization (HMO) and a university student population, Hooton et al. (5) demonstrated that the incidences of cystitis were approximately 0.5 and 0.7 per person per year, respectively. Based on national surveys estimating that 53 million women (including adolescents) are sexually active (6), Hooton and Stamm (7) suggested that many more millions of episodes of acute cystitis occur annually than are reported on the basis of data obtained from surveys of office visits.

UTIs are 14 times more common in women than in men (8). Stamey et al. (9,10) suggested some reasons for the increased risk for UTI in women: (a) the short female urethra; (b) the external one third of the urethra is continuously contaminated by pathogens from the vagina and rectum; (c) women do not empty their bladder as completely as men; and (d) passage of bacteria into the bladder with sexual intercourse. Thus, it is not surprising that clinicians providing health care for women are frequently called on to diagnose and treat the major forms of UTIs. Johnson and Stamm (11) estimate that an individual woman's lifetime risk of experiencing at least one UTI exceeds 20%.

Obstetrician-gynecologists and other health care providers for women have long recognized the frequency and potential seriousness of UTIs in pregnant and nonpregnant women. The introduction into clinical practice of quantitative urine culture by Kass revolutionized our concepts of the etiology, pathogenesis, and treatment of UTIs (12). This investigative work showed that significant bacteriuria can occur in the absence of clinical symptoms or signs of UTI and established quantitative microbiology as the indispensable laboratory aid for the diagnosis, follow-up, and confirmation of cure for UTI (12,13). Kass demonstrated that urinary bacterial counts on midstream voided urine specimens distinguished between contamination and infection with a high degree of accuracy. From this work evolved the accepted definition of ASB: the presence of 100,000 or more colonies of a bacterial pathogen per milliliter of urine on two consecutive clean-catch midstream voided specimens in the absence of signs or symptoms of UTI. A single catheterized specimen revealing more than 100,000 colonies per milliliter of a pathogen is sufficient to make such a determination. Because of the difficulty in obtaining clean-catch voided specimens, suprapubic bladder aspiration has been recommended by some investigators to confirm the presence of bacteriuria (9,14). Stamm et al. (15) and Latham et al. (16) demonstrated that in symptomatic UTIs, the isolation of aerobic Gram-negative bacilli of more than 10^2 colony-forming units (CFU) per milliliter represents bacteriuria.

There is a trend for an increasing prevalence of bacteriuria with increasing age (17,18). A significant increase in the rate of ASB occurs after the onset of sexual activity, and the prevalence of bacteriuria in women rises with age at a rate of approximately 1% for each decade of life (18). Nicolle et al. (19) documented the importance of sexual intercourse as a precipitating factor for UTIs in sexually active women. Fully 75% of UTI episodes in women with a history of recurrent UTIs occurred within 24 hours of coitus. Similarly, Ronald (20) estimated that at least two thirds of the acute episodes of UTIs in young sexually active women are attributable to coitus. The incidence of ASB is comparable for pregnant and nonpregnant women of the same socioeconomic group (8). Turck et al. (21) noted that the socioeconomic status of patients influenced the prevalence of bacteriuria. Although bacteriuria was present in only 2% of nonindigent patients, it was detected in 6.5% of indigent patients. Additional studies have confirmed this inverse relationship between socioeconomic status and prevalence of bacteriuria (22,23). Table 15.1 summarizes the factors associated with the development of bacteriuria in women.



Sex: Bacteriuria 14 times more common in women
Age: Prevalence of bacteriuria increases 1% per decade of life
Sexual activity:
Coitus facilitates movement of uropathogens from the introitus to the urethra
Socioeconomic status:
Prevalence of bacteriuria is inversely related to socioeconomic status; indigent women two to three times more likely to have bacteriuria
Sickle cell trait/disease:
Associated with twofold increase in prevalence of bacteriuria
Pathogenic factors of bacteria:
Fimbriae or pili (adherence), K antigen (antiphagocytic), hemolysin (cytotoxic), antimicrobial resistance (survival)
Diabetes mellitus
Immunosuppression

Source: From McNeasley SG. Treatment of urinary tract infection in pregnancy. Clin Obstet Gynecol 1988;31:480–482, with permission.

TABLE 15.1. FACTORS ASSOCIATED WITH BACTERIURIA IN WOMEN

Until recently, the factors that influence the risk of acquiring UTI have been identified in small case-control studies demonstrating wide ranges of risk estimates (5). In summary, these studies demonstrated that these factors included (a) recent sexual intercourse (19,20,27,28); (b) use of a diaphragm with spermicide (25,26,27,28,29 and 30); (c) delayed post–coital micturition (25,28,31,32); and (d) ABO blood group nonsecretor phenotype (33,34 and 35). In a large prospective study of sexually active young women, Hooton et al. (5) demonstrated that the risk of UTI is strongly and independently associated with recent sexual intercourse, recent use of a diaphragm with spermicide, and a history of recurrent UTI. In addition, these authors noted a strong dose-response relationship between the risk of UTI and both recent use of a diaphragm with spermicide and recent sexual intercourse. On the other hand, the risk of acute UTI was not associated with use of a cervical cap, ABO blood group nonsecretor phenotype, or delayed post–coital voiding.

Similar to the pathogenesis of gonococcal and chlamydial pelvic inflammatory disease, Hooton et al. (36) demonstrated a typical association between the onset of the last menstrual period and presentation with acute cystitis in young healthy women. More than 40% of women with an acute UTI presented at 8 to 15 days after the onset of their last menstrual period (UTIs caused by *Escherichia coli* and *Staphylococcus saprophyticus*) (36). Foxman et al. (37) recently suggested that uropathogens may be transmitted directly by sexual contact. In this preliminary study, the authors compared *E. coli* isolates from 19 women with UTI with *E. coli* found in random initial voided urine specimens from their most recent sex partner. *E. coli* was isolated from 4 of 19 male sex partners, and in each case, the *E. coli* from the male partner was identical by gel electrophoresis and bacterial virulence profile to that from his sex partner (37). However, this was a small cross-sectional study, and larger prospective, longitudinal studies are required. Smith et al. (38) noted that recent antimicrobial use increased a woman's risk for acute cystitis (for university students: risk, 2.57; 95% confidence interval [CI], 1.24–5.32; for those in an HMO: risk, 5.83; 95% CI, 3.17–10.70). The authors suggested this relationship resulted from altered indigenous urogenital flora and vaginal colonization with uropathogens.

Additional risk factors have addressed specific groups of patients. Schwartz et al. (39) examined risk factors associated with UTI in postpartum women. Increased risk for postpartum UTI was associated with African-American, Native American, or

Hispanic race/ethnicity (odds ratio [OR], 1.30; 95% CI, 1.03–1.64), unmarried status (OR, 1.33; 95% CI, 1.11–1.58), cesarean delivery (OR, 2.7; 95% CI, 2.27–3.20), tocolysis (OR, 3.30; 95% CI, 2.15–5.06), maternal renal disease (OR, 3.89; 95% CI, 1.80–8.41), and preeclampsia or eclampsia (OR, 5.02; 95% CI, 1.84–13.64) (39). In general, maternal conditions and procedures that predisposed to UTIs were those associated with urethral catheterization (39). Among patients with recurrent UTIs, Hopkins et al. (40) reported that the overall risk for women to develop recurrent UTIs was not associated with any single human leukocyte antigen (HLA), ABO, or Lewis phenotype.

Stapleton et al. (41) demonstrated that nonsecretors of blood group antigens who developed UTI were significantly more likely to be colonized rectally with adhesin-fimbriated *E. coli* than infected secretors (56% vs. 27%; $p = 0.042$) or uninfected nonsecretors (56% vs. 31%; $p = 0.046$). This large prospective study complements results of earlier studies that found that nonsecretors of blood group antigens are more prone to have recurrent UTIs (33,35).

Stamm and Raz (42) recently assessed the factors contributing to UTIs in postmenopausal women. In postmenopausal women (aged 50 to 70 years), the factors associated with UTI were (a) lack of estrogen, (b) nonsecretor status, (c) a history of UTI in the premenopausal period, (d) urinary incontinence, (e) presence of a cystocele, and (f) postvoid residual urine (42). Among older institutionalized women (older than 70 years), catheterization, urinary incontinence, antimicrobial exposure, and diminished mental status were most strongly related to risk of recurrent UTI (42). In part, the increased susceptibility of postmenopausal women to have UTIs is accounted for by a lack of estrogen, which results in a rise in vaginal pH level, disappearance of lactobacilli from the vaginal flora, and colonization of the vagina by enterobacteria, particularly *E. coli* (43). On the other hand, administration of estrogen has been shown to prevent recurrent UTI in postmenopausal women (43).

ETIOLOGY

Most of the organisms responsible for UTIs are considered part of the normal fecal flora. *E. coli* is the etiologic agent in approximately 80% to 90% of acute infections (1,7,8,10,36,44,45,46 and 47). Other Gram-negative facultative bacteria such as *Klebsiella, Proteus, Enterobacter,* and *Pseudomonas,* as well as Gram-positive bacteria such as *S. saprophyticus,* group B streptococcus, and the enterococcus are responsible for the remainder. Recently *S. saprophyticus* has been demonstrated to be the second most common cause of UTI in young sexually active women (7,44,45). In the study by Latham et al. (45), this organism accounted for 11% of UTIs seen in female college students. In addition, *Gardnerella vaginalis* is increasingly recognized as a pathogen in UTI in women. This is not a surprise because *G. vaginalis* is a common component of the normal vaginal flora.

In patients who have received antibiotics, have undergone urologic instrumentation, or have chronic recurrent infections, the causative organism is more likely to be *Klebsiella, Enterobacter, Proteus, Pseudomonas, Serratia,* or the enterococcus.

PATHOGENESIS

The association between the enteric flora and urinary pathogens has led to the

hypothesis that the mechanism of acquiring UTIs is by an ascending route of infection from the bowel to the vaginal vestibule and then to the urethra and ultimately the bladder (7,8,10,48,49 and 50). Stamey and Sexton (51) noted that the vaginal vestibule of women with recurrent bacteriuria had a higher incidence of colonization by enterobacteria between episodes than the vestibule of women without recurrent UTIs. Subsequently, Fowler and Stamey (52) demonstrated that *E.coli* adheres more readily to introital epithelial cells in women with recurrent UTIs. Stamey et al. (53) reported that colonization of the vaginal introitus with Gram-negative enteric bacteria was associated with absence of antibody in the cervicovaginal secretions.

More recently, Stapleton et al. (41) demonstrated that persistent rectal colonization with *E. coli* containing the adhesins P and F (i.e., P- and F-fimbriated *E. coli*) is significantly associated with persistent vaginal *E. coli* colonization with these same fimbriated organisms. However, persistent colonization with such *E. coli* was as common in women with and without recurrent UTIs. Moreover, in their longitudinal study, these authors noted that persistent vaginal or rectal colonization with fimbriated *E. coli* infrequently resulted in symptomatic UTI, and symptomatic UTIs were preceded by vaginal colonization with these fimbriated *E. coli* strains for 1 week or more in only a few cases (41). As a result, Stapleton et al. (41) concluded that although urovirulence factors (P- and F-adhesins) provide *E. coli* with a selective advantage, once it reaches the vaginal and bladder epithelium, additional factors such as spermicide exposure, sexual intercourse, voiding behavior, bacterial composition of the vaginal flora, and local immune factors play equally important roles in determining whether an *E. coli* isolate colonizing the vaginal mucosa is eradicated or persists and enters the bladder to initiate the infectious process.

Colonization of the introitus with uropathogens is a critical step in the pathogenesis of UTI. Such colonization is influenced to a large extent by the microbial ecosystem of the vagina (29). The normal vaginal microflora predominated by lactobacilli and the associated acidic pH level of the vagina prevent establishment of prolonged colonization of the vaginal introitus with uropathogenic *E. coli* (54). Stamm et al. (55) suggested that there are three specific factors that can alter the normal vaginal microflora in such a manner as to predispose to *E. coli* colonization and increase the risk of acute uncomplicated cystitis. These are (a) diaphragm and spermicide use, (b) antimicrobial exposure, and (c) lack of estrogen (e.g., in postmenopausal women).

The active component of spermicides, nonoxynol 9, is an active microbicide against many lactobacilli and *G. vaginalis* strains, whereas *E. coli* and other pathogens are highly resistant to this effect (56). Hydrogen peroxide–producing strains of *Lactobacillus* were more susceptible to nonoxynol 9 than nonproducers (56). In addition, nonoxynol 9 enhanced adherence of *E. coli* to vaginal epithelial cells (56). These mechanisms explain the epidemiologic studies demonstrating that diaphragm-spermicide and spermicide use alone are associated with an increased risk of UTI, ASB, and vaginal colonization with *E. coli* (29,54). Thus, spermicide use appears to provide a selective advantage in colonizing the vagina with uropathogens such as *E. coli* (56). Many antimicrobial agents, particularly the b lactams (penicillins and cephalosporins), have an adverse effect on the normal vaginal flora and facilitate colonization with *E. coli* and other uropathogens. In postmenopausal women, lack of estrogen is associated with markedly reduced *Lactobacillus* colonization, an increased vaginal pH level, and an increased *E. coli* colonization of the vagina

(42,43,57). As a result, the risk of acute uncomplicated UTI is increased tenfold in postmenopausal women not receiving hormone replacement therapy (57). Raz and Stamm (43) reported that these changes can be reversed, and the risk for UTI decreased in postmenopausal women with the use of intravaginal topical estrogen therapy.

E. coli is clearly the most common uropathogen and is responsible for 80% of acute uncomplicated cystitis and approximately one third of complicated UTIs (1,7,55,58). Not surprisingly, most studies on the pathogenesis of UTIs have focused on *E. coli,* and the virulence characteristics of uropathogenic *E. coli* have been extensively studied in women (59,60,61 and 62). These studies have demonstrated that the *E. coli* strains causing acute UTIs comprise a unique group of uropathogens defined by the O : K : H serotype and possessing virulence determinants that enable these microorganisms to colonize and infect the urinary tract (59,60,61 and 62). These virulence factors include adherence factors (P, type 1, S, Dr fimbriae), toxins (lipopolysaccharide [LPS], hemolysin), aerobactin, invasion factors, and serum resistance (60,62).

Svanborg and Godaly (62) have recently reviewed the role of bacterial virulence in the pathogenesis of UTI. Bacterial adherence is a key step in the pathogenesis of UTI by which uropathogenic strains of *E. coli* colonize mucosal sites (63,64). This attachment is regulated by interactions between bacterial adhesins and receptors on host cells (65). Uropathogenic *E. coli* possesses two major types of adhesins: surface pili or fimbriae and outer membrane proteins (62). he fimbriae-associated adhesins of uropathogenic *E. coli* are known as lectins, which are carbohydrate binding proteins that recognize host cell glycoconjugate. P fimbriae lectins recognize epitopes of the globoserides of glycolipids (62,65). S fimbriae lectins and type 1 fimbriae bind glycoconjugates with sialic acid residues and mannose residues on the Tamm-Horsfall protein, secretory immunoglobulin A, and fibronectin, respectively (62).

The most important of these virulence determinants are P fimbriae that mediate specific binding of *E. coli* to Galá 1-4 Gal receptors on uroepithelial cells (54,65). It has been demonstrated that certain strains of *E. coli* that commonly express P fimbriae are more commonly isolated from the urine of patients with acute pyelonephritis than those with acute cystitis or ASB (54,59,66,67 and 68). In addition, whereas only 10% to 20% of fetal strains of *E. coli* possess P fimbriae, approximately 50% to 60% of strains associated with acute cystitis possess P fimbriae (69). P fimbriae are believed to facilitate ascent of *E. coli* to the upper urinary tract by specific binding to receptors on uroepithelial cells (61). P fimbriae also enhance the inflammatory response in the urinary tract to *E. coli,* resulting in secretion of significantly more interleukin-6 (IL-6) than seen with nonfimbriated strains (54,70,71).

Type 1 fimbriae occur in both virulent and avirulent isolates of *E. coli* (54). The type 1 fimbriae appear to contribute to virulence when they are present in association with an already established virulent uropathogen (54). In such a situation, type 1 fimbriae aid in the persistence of *E. coli* in the urinary tract, induce more severe infection, and induce a greater inflammatory response (54,72).

Uropathogenic *E. coli* contain LPSs in their outer membrane and produce hemolysin and aerobactin (54). Strains of *E. coli* that express aerobactin are isolated more

frequently from the urine of patients with acute pyelonephritis than from those with cystitis or ASB (73,74). Hemolysin production and resistance to the bactericidal effect of serum are also more common among urinary isolates than among fecal isolates from healthy patients (68,69,75). It is believed that aerobactin-mediated uptake of iron promotes bacterial growth and persistence of bacteria in tissue (60,73). Hemolysins are cytotoxic proteins that play a role in tissue injury secondary to cytotoxic effects (54,69,75).

In addition to their ability to lyse erythrocytes, hemolysins are toxic to a wide range of cells (e.g., polymorphonuclear [PMN] leukocytes, monocytes). *E. coli* a- hemolysin has been shown to produce injury to renal tubular cells *in vitro* (54). Thus, although hemolysin does not enhance persistence of uropathogens in the upper urinary tract, Svanborg and Godaly (62) suggested that hemolysin may aid in producing the mucosal damage that is required for invasive disease to occur.

LPSs contain polysaccharide, a core region and lipid A as an anchor. The lipid A moiety of LPS contains toxic, inflammatory, and immunomodulatory properties (54). Thus, LPS present on the surface of attached bacteria may cause the acute stage of symptomatic UTI (54). Polysaccharide capsules are well-recognized virulence factors for many bacteria (e.g., *Haemophilus influenzae, Neisseria meningitidis,* and *Streptococcus pneumoniae*). Polysaccharide capsules act by preventing access to bacteria by complement and phagocytic leukocytes (54).

Once they spread to the urinary tract, uropathogenic clones of *E. coli* (and other uropathogens) overcome local host defenses such as urine flow, secreted receptor analogs, which trap fimbriated bacteria, and bactericidal molecules in the urine and mucosa (54). Once these defenses are bypassed, uropathogenic bacteria target the mucosa of the urinary tract, where they elicit an inflammatory response in which cytokines and proinflammatory factors are produced (62,70,71). As the result of systemic spread of interluekin-6 (IL-6), fever and the acute phase response may occur. Release of chemotactic cytokines (e.g., IL-8) recruits PMN granulocytes to the mucosal surface, which in turn clears bacteriuria (62). In acute pyelonephritis, approximately 30% of patients develop bacteremia secondary to bacterial invasion through the mucosa into the bloodstream (62). The localization and magnitude of the inflammatory response elicited determines the clinical presentation of UTIs (62). For instance, in acute pyelonephritis, inflammation of the kidney occurs in association with generalized signs of inflammation such as fever and leukocytosis (62).

The pathogenesis of acute cystitis and ASB is less well delineated (62). There are no bacterial virulence factors that identify strains of *E. coli* associated with cystitis (62). Svanborg and Godaly (62) have proposed that the clinical syndrome of acute cystitis reflects host response mechanisms that differ from those seen in pyelonephritis, and that cystitis-prone patients have a local accumulation of most cells in the bladder mucosa. Although ASB may be associated with local inflammation in the bladder, the magnitude of the inflammatory response is insufficient to produce symptoms (62).

It is estimated that approximately 20% of women with acute cystitis subsequently develop recurrences (1). In the past, it was believed that more than 90% of recurrences in young women were episodes of exogenous reinfection (1,56). More recently, it was suggested that most of these recurrences are the result of a single infecting *E. coli* strain, even over a long time (7). Most likely, this occurs secondary to persistent *E. coli* in the vagina and feces despite eradication of the organism from

the urinary tract. Only rarely are anatomic or functional abnormalities of the urinary tract responsible for recurrent UTIs (1). The *E. coli* strains causing recurrent UTIs do not have urovirulence determinants that differ from those associated with acute episodes of cystitis (1). Similarly, no host defense differences have been demonstrated in patients with recurrent UTI versus those with acute UTI (1). On the other hand, genetic differences among patients may play a role in the pathogenesis of recurrent UTI. Women who are nonsecretors (do not secrete blood group antigens) are more likely to have recurrent UTIs and their uroepithelial cells possess specific *E. coli*–binding glycolipids, which are absent in women who do not secrete blood group antigens (33,40,41,76).

Sobel (77) recently reviewed the role of host defenses in the pathogenesis of UTI. Table 15.2 lists the antimicrobial host defenses in the urinary tract of women. Normal urine contains several components that are inhibitory for bacteria, including urea, organic acids, high pH level, and low osmolality (77). On the other hand, the growth of *E. coli* is facilitated by glucosuria and the lower urine pH level during pregnancy (77). Micturition and efficient bladder emptying are major defense mechanisms against developing UTI (78). Bladder mucosa contains intrinsic antibacterial activity, probably secondary to the production of bactericidal molecules by epithelial cells (77,79,80). Sig A diminishes attachment of bacteria to uroepithelial cells (77). In addition, urine contains several molecules that are soluble receptor analogs that act as competitive inhibitors of adherence of uropathogens to epithelial cells (77,81). These molecules include (a) Tamm-Horsfall protein, which is secreted by tubular cells into urine and inhibits attachment of type 1 fimbriated *E. coli* (82); (b) mucopolysaccharide lining the bladder plays an important role in preventing bacterial attachment to the bladder mucosa (83); and (c) various low-molecular-weight oligosaccharides that are potent inhibitors of *E. coli* type 1–mediated adherence (84).

Urine (osmolality, pH, organic acid levels)	Inflammatory response
Urine flow and micturition	polymorphonuclear leukocytes
Urinary tract mucosa (bactericidal activity, cytokines)	Cytokines
Urinary inhibitors of bacterial adherence	Immune system
Tamm-Horsfall protein	Humoral
Bladder mucopolysaccharide	Cell mediated
Low-molecular-weight oligosaccharide	
Sig A	
Lactoferrin	

Source: From Sobel JD. Pathogenesis of urinary tract infection: role of host defenses. Infect Dis Clin North Am 1997;11:531–549, with permission.

TABLE 15.2. ANTIBACTERIAL HOST DEFENSES IN THE URINARY TRACT OF WOMEN

As in other anatomic sites, bacteria cause an inflammatory response in the urinary tract, which is site specific (62,77). Thus, in acute cystitis, a localized inflammatory response occurs, whereas in acute pyelonephritis both a localized and a systemic inflammatory response are seen. After adherence to uroepithelial cells, bacteria induce a mucosal inflammatory response in which PMNs infiltrate into the mucosa

and ultimately the urine (77). The primary role of these PMNs is to limit tissue invasion (77). Secretion of PMN chemoattractants (i.e., IL-8) and expression of adhesion molecules (intercellular adhesion molecule-1) that facilitate transepithelial migration of PMNs by uroepithelial cells are responsible for this PMN response (77,85). As part of the inflammatory response, cytokines are elaborated in response to bacterial adhesion by uroepithelial cells (62,70,71,77). IL-6 production is most prominent, but IL-1 and IL-1b are also present. This cytokine response is enhanced by adherence of type 1 and P fimbriae to uroepithelial cells (70,77).

Evidence for urinary tract immune mechanisms including mucosal and systemic antibody response and cell-mediated immune response has been reported (77). However, the protective role the immune response plays in resistance to UTI remains unclear (77). Acute pyelonephritis is followed by a specific serum and urinary antibody response by 7 to 10 days after the onset of infection (86). The response seen with pyelonephritis is significantly greater than that with acute cystitis (87). Both serum and urinary antibody responses occur. The serum response is characterized by immunoglobulin M and immunoglobulin G antibodies to O and K antigens and to P fimbriae (77). Urinary antibodies are primarily Sig A, also against O and K antigens and fimbriae (77). As noted by Sobel (77), the main protective function of these serum and urinary antibodies is with invasive parenchymal infection in pyelonephritis. The protective role of cell-mediated immunity is even less clear in UTI (77). Few T lymphocytes are present in normal urinary tract mucosa, and there is no evidence of increased susceptibility to or increased severity of UTI in patients with severe defects in cell-mediated immunity (77).

Certain host factors have been identified that predispose to UTIs. These include obstruction to urine flow, diabetes mellitus, and aging (77). However, most symptomatic lower (cystitis) and upper (pyelonephritis) UTIs in healthy adults (predominantly women) occur in the absence of structural or functional abnormalities of the urinary tract. Studies assessing risk factors for UTI have produced various theories, including minor degrees of urinary obstruction, bladder overdistention, defective immune and antiadherence mechanisms, increased receptivity of uroepithelial cells for bacterial attachment, and behavioral factors that promote vaginal colonization with uropathogens (5,20,27,28,29,30,31,32,33,34,35,36,37 and 38,88). Sobel recently reviewed these host factors and provided a concept of the pathogenesis of UTI in women (Fig. 15.1). In this model, genetic factors lead to increased susceptibility for fecal colonization with P-fimbriated *E. coli.* In turn, this results in enhanced colonization of the vagina, vestibule, and periurethral areas with uropathogens. Behavioral risk factors (e.g., spermicide use, infrequent voiding, and estrogen deficiency) also enhance uropathogen colonization of the vagina, vestibule, and periurethral areas. Vaginal intercourse facilitates the ascension of uropathogens to cause bladder bacteriuria.

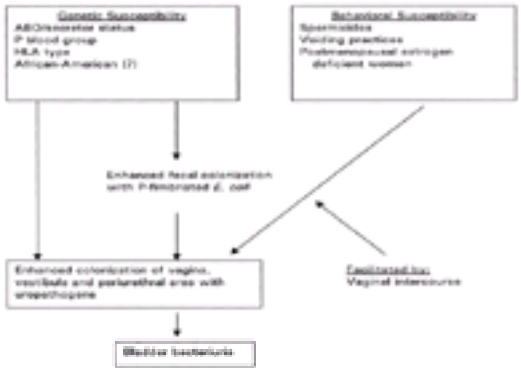


FIGURE 15.1. Host factors in the pathogenesis of urinary tract infections in women. (From Sobel JD. Pathogenesis of urinary tract infection: role of host defenses. *Infect Dis Clin North Am* 1997;11:531–549, with permission.)

DIAGNOSIS

The absolute criterion for the diagnosis of UTI is the microbiologic confirmation of pathogenic bacteria in the urinary tract above the urethra Bacteriuria was traditionally defined as the presence of $^{3}10^{5}$ CFUs per milliliter of urine from two consecutive first void clean-catch urine specimens (12,13,89). The presence of pyuria suggests infection but is not diagnostic of UTI.

As described already, ASB is diagnosed on the basis of quantitative cultures with more than 100,000 colonies of a pathogen per milliliter of clean-voided urine specimens in asymptomatic patients. Direct suprapubic bladder aspiration is an excellent technique for obtaining meaningful urine cultures. The presence of any bacterial pathogen in a suprapubic aspirate is indicative of a UTI. Stamey et al. (9) claimed to have had no complications occur in more than 2,500 bladder aspirations. These authors noted with suprapubic bladder aspiration that one third of urinary infections were associated with bacterial counts of less than 10^{5} bacteria per milliliter of urine. Subsequently, Stamm et al. (15) and Latham et al. (16) proposed new diagnostic criteria for uncomplicated UTI in acutely dysuric women. They noted that 30% to 50% of patients with acute lower urinary tract infections characterized by dysuria, urgency, and frequency did not meet the more than 10^{5} bacteria per milliliter criterion for infection but had pathogenic aerobic Gram-negative bacilli present with suprapubic taps. They found the best diagnostic criterion to be $^{3}10^{2}$ bacteria per milliliter, with a sensitivity of 0.95, a specificity of 0.85, and a high predictive value (0.88) among symptomatic women. They suggested that the most efficient approach for the diagnosis of symptomatic UTIs was to use rapid screening tests for pyuria to guide dual-culturing method to detect 10^{2} CFU/mL plus standard culture for specimens without pyuria.(16). Alternatively, The Infectious Diseases Society of America (IDSA) provided consensus definitions for the use in antimicrobial treatment studies (90). For cystitis, it recommended $^{3}10^{3}$ CFU/mL (sensitivity, 80%; specificity, 90%), and for pyelonephritis $^{3}10^{4}$ CFU/mL (sensitivity, 90% to 95%). These concentrations were chosen over $^{3}10^{2}$ CFU/mL because the greater concentrations can be identified by standard microbiologic techniques in most clinical laboratories

(7).

Once a sample of urine is obtained, to confirm a diagnosis of UTI, the specimen must be rapidly brought to the microbiology laboratory or refrigerated. A delay of more than 2 hours will result in an erroneous high bacterial count (91). The urine should be cultured on blood agar, as well as on deoxycholate, eosin methylene, or MacConkey agar for Gram-negative rods. Quantitation of bacteria can be accomplished by means of standard dilutions, using either the pour plate or the streak spread plate technique. Many clinicians have been reluctant to test all symptomatic patients or to screen all pregnant patients for bacteriuria by culture methods because of the cost (92,93,94 and 95). As a result, office testing for bacteriuria has been suggested as an alternative to using quantitative urine cultures. However, when compared with quantitative cultures, office screening systems such as Testuria (Ayerst Laboratories), Bacturcult (Wampole Laboratories), and Microstix-3 (Ames) correctly predicted only 62.5% to 87.5% of bacteriuria (96). Moreover, in pregnant women, these tests were associated with unacceptably high false-positive and false-negative results (96). In addition, alternative bacteriuria screening tests such as Bac-T-Screen (Marion Laboratories), which measures bacteria entrapped on a filter, and Chemstrip LN (Biodynamics) had high false-positive rates and a poor sensitivity, respectively (97).

Recent reviews have also cautioned against rapid detection methods for bacteriuria (7,93). Hooton and Stamm (7) noted that rapid tests such as the nitrite test, catalase tests, filtration-based screening, and bioluminescence screening methods currently available lack adequate sensitivity, particularly for “low-count” UTI (i.e., $^{3}10^{2}$ or $^{3}10^{3}$ CFU/mL). Millar and Cox (93) similarly claim that none of the new rapid screening techniques for UTI have all the requirements for a good screening test (excellent sensitivity and good specificity). This study included Uricult dipslide paddle (Orion Diagnostica, Helsinki, Finland), Cult-Dip Plus (Merck, Germany), Uristat test (Shields Diagnostics Ltd., Dundee, Scotland), and bioluminescence assays. Hagay et al. (98) recently reported excellent sensitivity (100%) good specificity (81%), and excellent negative predictive value (100%), but poor positive predictive value (30%) with a rapid enzymatic urine screening test (Uriscreen [Diatech Diagnostics Ltd., Israel]). Because of the poor positive predictive value, urine cultures should be obtained in patients with positive screening test results. Essentially, all cases of ASB are detected and urine culture can be avoided in patients with negative test results, thus providing substantial cost savings (93).

In symptomatic patients, frequency, urgency, and dysuria are usually associated with cystitis, whereas fever, chills, and flank pain are additionally associated with pyelonephritis. However, these signs and symptoms are not specific for the localizing site of infection (i.e., bladder or kidney). Comparison of the clinical features of asymptomatic and symptomatic UTI is presented in Table 15.3.

Urinary Tract Infection	Clinical Manifestations	Pyuria	Bacteriuria	White Blood Cell Casts	Leukocytosis	Urine Culture (CFU/mL)
Asymptomatic bacteriuria	None	+	+	-	-	≥10⁵ (clean catch)
Acute cystitis	Frequency, urgency, dysuria	+	+	-	-	≥10⁵ (catheterized) or ≥10⁵ (clean catch)
Acute pyelonephritis	Frequency, urgency, dysuria plus fever, chills, flank pain, costovertebral angle tenderness	+	+	+	+	≥10⁵ (catheterized) or >10⁵ (clean catch)

TABLE 15.3. CLINICAL MANIFESTATIONS AND LABORATORY ABNORMALITIES IN URINARY TRACT INFECTIONS

Although classic teaching described the ascending route as the most frequent for UTIs, it has also been shown that the upper urinary tract may be the source of bacteriuria in many women (24). Various methodologies have been employed in the localization of UTIs (99). Direct methods include ureteric catheterization for culture. However, most investigators have relied on indirect methods such as measurement of maximum urinary concentrating ability (100,101), serum antibody titers against infecting organisms (102,103 and 104), pattern of response to therapy (8,103), b-glucuronidase excretion in urine (101), bladder washout techniques (105), and antibody-coated bacteria in the urinary sediment (106,107). The role of antibody-coated bacteria in localization of UTI site has received the most attention. Thomas et al. (106) demonstrated that bacteria from the kidney are coated with antibody, whereas organisms limited to the bladder or urethra are not. In general, 40% to 50% of bacteriuria cases are believed to be of renal origin. However, use of the antibody-coated test has not received widespread clinical use and is chiefly used in research studies.

SYMPTOMATIC URINARY TRACT INFECTIONS IN NONPREGNANT WOMEN

Acute Uncomplicated Cystitis In Young Women

As noted by Stamm and Hooton (1), a very narrow spectrum of microorganisms is involved in the etiology of acute uncomplicated cystitis (Fig. 15.2). *E. coli* accounts for 80%, *S. saprophyticus* for 10% to 15%, and other organisms such as *Klebsiella* sp and *Proteus mirabilis* 5% to 10% (1). In addition, these etiologic agents have very predictable antimicrobial susceptibility profiles (1). Risk factors for the development of acute uncomplicated UTI have been identified, including sexual intercourse, use of a diaphragm and spermicide, spermicide alone, delayed post–coital micturition, history of recent UTI, and use of selected antimicrobials that alter the normal vaginal flora (Table 15.4) (5,25,26,27,28,29,30,31,32,33,34,35,36,37 and 38).

FIGURE 15.2. Etiology of acute uncomplicated cystitis in young women. *Other pathogens are occasionally isolated, such as *Klebsiella* sp, *Proteus mirabilis,* and other microorganisms.

Sexual intercourse
Diaphragm and spermicide use
Spermicide alone
Delayed post-coital micturation
History of recent urinary tract infection
Use of selected antimicrobial agents

TABLE 15.4. RISK FACTORS FOR ACUTE UNCOMPLICATED CYSTITIS IN WOMEN

Women with acute uncomplicated cystitis typically present with dysuria. However, acute dysuria may be due to three types of infection: (a) acute cystitis due to enterobacteria, particularly *E. coli*; (b) acute urethritis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*; and (c) vaginitis due to *Candida* or *Trichomonas vaginalis* (1,7,11). Table 15.5 summarizes the approach to differentiating these causes of dysuria based on presenting symptoms, signs, and urinalysis results.

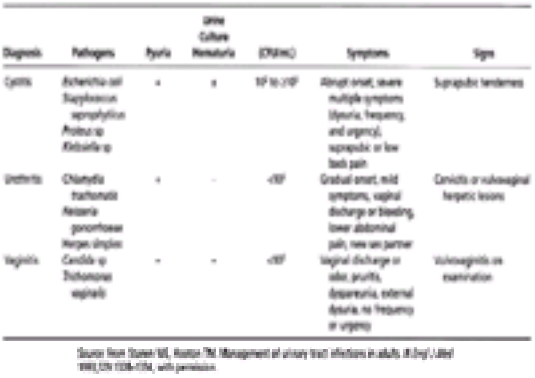


TABLE 15.5. DIFFERENTIAL DIAGNOSIS OF ACUTE DYSURIA IN YOUNG WOMEN

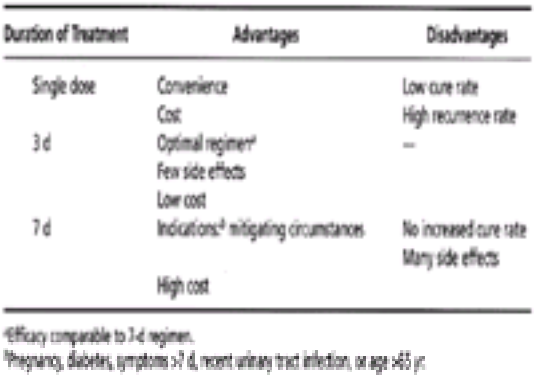
Traditionally, the diagnosis of acute uncomplicated cystitis was based on detecting 10^2 to more than or equal to 10^5 colonies per milliliter of a uropathogen in a clean-catch midstream urine specimen. However, current recommendations advocate establishing the diagnosis of acute uncomplicated cystitis with an abbreviated laboratory workup (1,4,7,108,109). In patients with typical symptoms (Table 15.5), a diagnosis of acute cystitis is presumed if pyuria is present on leukocyte esterase dipstick testing or microscopy (1,7). Urine culture is not necessary in young women with typical symptoms of acute cystitis. In addition, because the causative microorganisms and their antimicrobial susceptibility patterns are so predictable in young women with acute cystitis, the abbreviated diagnostic workup can be followed by a short course of empiric antimicrobial therapy. No follow-up visit or culture after therapy is recommended unless symptoms persist or recur (1,7). This approach has been demonstrated to be clinically efficacious, safe, and cost-effective (4,108). An alternative approach is to exclude any laboratory testing and treat empirically for acute cystitis based only on the presence of typical symptoms. However, if pyuria is absent in the face of typical symptoms suggestive of acute cystitis, or if mitigating clinical circumstances (Table 15.6) are present, culture should not be omitted (1). Of note for providers of maternity care, pregnant women are among those in whom culture is recommended for detection of UTI.

1. Pregnancy
2. Diabetes
3. Symptoms lasting >7 d
4. Recent urinary tract infection
5. Age >65 yr

TABLE 15.6. CLINICAL CIRCUMSTANCES THAT WARRANT INITIAL URINE

CULTURE IN PATIENTS WITH SYMPTOMS OF ACUTE CYSTITIS

Identification of the optimal treatment for uncomplicated acute cystitis in young women has been a controversial issue. The traditional approach of a 7- to 10-day antimicrobial regimen was challenged and single-dose therapy was introduced about 10 years ago. However, the efficacy and recurrence rate of single-dose therapy also has subsequently been challenged and current recommendations have focused on use of a 3-day regimen of antimicrobial therapy for treatment of acute uncomplicated cystitis in young women. Stamm and Hooton (1) summarized the advantages and disadvantages of varying lengths of antimicrobial treatment for acute uncomplicated cystitis (Table 15.7). In summary, for most antimicrobial agents, a 3-day regimen appears to be optimal, with efficacy similar to that of 7-day regimens and fewer side effects and lower cost (1). Single-dose therapy results in lower cure rates and more frequent recurrences, particularly with amoxicillin or oral cephalosporins, although 7-day regimens are no more effective than 3-day courses and increase cost and side effects (1,3,7,110,111,112,113,114,115,116 and 117).



Duration of Treatment	Advantages	Disadvantages
Single dose	Convenience	Low cure rate
	Cost	High recurrence rate
3 d	Optimal regimen[a]	—
	Few side effects	
	Low cost	
7 d	Indications[b]: mitigating circumstances	No increased cure rate
		Many side effects
	High cost	

[a]Efficacy comparable to 7-d regimen.
[b]Pregnancy, diabetes, symptoms >7 d, recent urinary tract infection, or age >65 yr.

TABLE 15.7. COMPARISON OF ANTIMICROBIAL REGIMENS OF VARYING LENGTH FOR TREATMENT OF ACUTE UNCOMPLICATED CYSTITIS IN YOUNG WOMEN

If single-dose therapy is selected, be aware that the best results have been reported with trimethoprim-sulfamethoxazole, fluoroquinolones, and fosfomycin tromethamine (3,113,114 and 115,117). Amoxicillin and oral cephalosporins are rapidly excreted and often ineffective as single-dose therapy, particularly in patients with subclinical upper urinary tract involvement (3,110,113). Ronald et al. (118) reported that up to 30% of patients presenting as acute cystitis have occult renal infection. In addition, a high failure rate has been reported with single-dose fluoroquinolone regimens in cases of acute cystitis due to *S. saprophyticus* (113,115). Seven-day regimens should be reserved for use in patients with mitigating factors that are associated with lower cure rates when 3-day regimens are used (Table 15.8) (1); pregnancy is one of these factors. These are the same factors in which culture should be obtained before

therapy.

1. Pregnancy
2. Diabetes
3. Symptoms for >7 d
4. Recent urinary tract infection
5. Diaphragm/spermicide use
6. Age >65 yr

TABLE 15.8. PATIENTS IN WHOM 7-D REGIMENS OF ANTIMICROBIAL THERAPY ARE RECOMMENDED FOR THE TREATMENT OF ACUTE CYSTITIS

In the United States, increasing resistance to some of the antimicrobial agents frequently used for the treatment of acute uncomplicated cystitis has occurred (Fig. 15.3) (1). One third of bacterial strains causing community-acquired acute uncomplicated cystitis are resistant to amoxicillin and sulfonamides (3,7,110,111,113,115,117). Approximately 15% to 20% of these uropathogens are resistant to nitrofurantoin (3,110,111,112 and 113,115). Studies in Seattle demonstrate a trend toward increased susceptibility of uropathogens to nitrofurantoin (4% resistance) (7). Increasing resistance is also being seen to trimethoprim-sulfamethoxazole; this varies geographically and ranges from 5% to 15% (1,3,7,110,111,113,114 and 115,117). The increased resistance to trimethoprim-sulfamethoxazole is cause for great concern (7). Some studies have demonstrated resistance prevalences among community-acquired *E. coli* strains of as high as 60% (most 5% to 15%) (7). Most disturbing are the longitudinal studies demonstrating increasing resistance rates over time for trimethoprim and trimethoprim-sulfamethoxazole (7,119). In a recent study of uncomplicated pyelonephritis, Talan et al. (120) noted that 18% of *E. coli* strains were resistant to trimethoprim-sulfamethoxazole. On the other hand, resistance to fluoroquinolones is low and remains less than 5% (1,7,117). However, a word of caution was noted by Gruneberg (121), who reported that 10% of strains in general practice in the United Kingdom were resistant to fluoroquinolones.

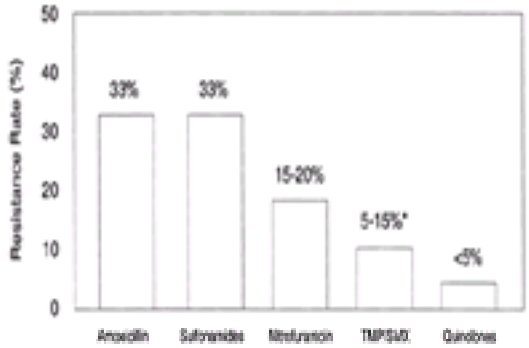


FIGURE 15.3. *In vitro* resistance among pathogens from women with acute uncomplicated cystitis resistance. *Trimethoprim-sulfamethoxazole resistance varies geographically and is increasing.

As discussed already, the impact of antimicrobial therapy on the vaginal flora also plays a role in eradicating bacteriuria (1,19). Trimethoprim-sulfamethoxazole is present in vaginal secretions in high concentrations that eradicate *E. coli* but have minimal effect on the normal vaginal flora, particularly lactobacilli and anaerobic flora (1,112). Single-dose regimens with trimethoprim-sulfamethoxazole or fluoroquinolones are less effective than 3-day or 7-day regimens at eradicating *E. coli* from the vagina (1). Moreover, when used in multiday regimens, b lactams have a high likelihood of altering the vaginal flora by eradicating lactobacilli and predisposing patients for recurrent UTIs. Shown in Table 15.9 are the relative benefits and drawbacks to varying durations of antimicrobial therapy for acute cystitis. Clearly the 3-day regimen maximizes the efficacy and minimizes adverse effects (1). Stamm and Hooton (1) concluded that trimethoprim-sulfamethoxazole and trimethoprim are the optimal choices for empiric 3-day therapy for acute uncomplicated cystitis (Table 15.10). Their recommendation was based on current susceptibility patterns of uropathogens, duration of urinary excretion, antimicrobial effects on the vaginal flora, safety, and cost (1). Although they noted that the fluoroquinolones are also very effective and well tolerated in 3-day regimens, these agents are more expensive and should be reserved for use in patients with recurrent UTI, in patients in whom treatment fails, in patients allergic to other agents, and in patients with infections caused by uropathogens resistant to other antimicrobials (1). In geographic areas with high trimethoprim-sulfamethoxazole resistance rates (i.e., more than 10% to 20%), fluoroquinolones should be used as empiric therapy of acute uncomplicated cystitis (1,7,117). These authors also reported that less satisfactory results occurred with 3-day regimens of amoxicillin, oral cephalosporins, or nitrofurantoin, compared with trimethoprim-sulfamethoxazole for the management of acute uncomplicated cystitis (116).

	Single-dose Regimen	3-d Regimen	7-d Regimen
Efficacy			
Trimethoprim-sulfamethoxazole/ quinolones	+++	++++	++++
β-Lactams	++	++	++
Effect on vaginal-fecal flora	+	+++	++++
Side effects	+	+	+++
Cost	+	++	++++

+, minimal; ++, moderate; +++, marked; ++++, maximal.

TABLE 15.9. LENGTH OF THERAPY FOR ACUTE CYSTITIS: RELATIVE BENEFITS AND ADVERSE EFFECTS

1. Trimethoprim-sulfamethoxazole 160/800 mg q12h
2. Trimethoprim 100 mg q12h
3. Quinolones
   a) Ciprofloxacin 250 mg q12h
   b) Enoxacin 400 mg q12h
   c) Lomefloxacin 400 mg q24h
   d) Ofloxacin 200 mg q12h
   e) Norfloxacin 400 mg q12h
   f) Fleroxacin

TABLE 15.10. RECOMMENDED 3-D REGIMENS FOR ACUTE UNCOMPLICATED CYSTITIS IN YOUNG WOMEN

Recently the IDSA published guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis (117). In summary, the IDSA noted that in otherwise healthy adult nonpregnant women with acute uncomplicated cystitis, single-dose therapy is generally less effective than the same antimicrobial agent used for longer durations (A, I). Most antimicrobial agents given for 3 days are as effective as the same antimicrobial agent given for a longer duration (A, I). Trimethoprim-sulfamethoxazole for 3 days is considered the current standard therapy (A, I). Trimethoprim alone (A, II) and ofloxacin (A, I) are equivalent to trimethoprim-sulfamethoxazole; other fluoroquinolones (e.g., norfloxacin, ciprofloxacin, and fleroxacin) are probably of similar effectiveness (A, II). However, because fluoroquinolones are more expensive, and to postpone emergence of resistance to these drugs, fluoroquinolones are not recommended as initial empiric therapy for acute uncomplicated cystitis, except in communities with high rates of resistance (more than 10% to 20%) to trimethoprim-sulfamethoxazole among uropathogens. When given for 3 days, b lactam antimicrobial agents are less effective than trimethoprim-sulfamethoxazole or fluoroquinolones (E, I). Nitrofurantoin and fosfomycin may become more useful as

resistance to other agents increase (B, I).

Route posttreatment test of cure culture is not recommended with acute uncomplicated cystitis (7). The costs to detect cases of ASB are considerable and the benefit of detecting and treating ASB in healthy women has only been demonstrated in pregnancy and before urologic surgery or instrumentation (7). When symptoms do not resolve or recur within 2 weeks of treatment, a urine culture and susceptibility testing should be performed (7). Re-treatment is based on the results, and a 7-day course of therapy is initiated.

Recurrent Cystitis

After an initial episode of acute cystitis in young women, UTIs recur in roughly 20% (1). Most (more than 90%) of recurrences in young women are episodes of exogenous reinfection (57,122). Rarely (less than 10%), recurrences are due to occult renal infection or anatomic or functional abnormalities of the urinary tract (123). As discussed already (in the section on pathogenesis), the use of spermicides (with our without a diaphragm) has been associated with recurrent UTIs secondary to induction of *E. coli* colonization of the vagina by spermicides (54). Recurrent infections are also more common among nonsecretors—that is, women who do not secrete blood group antigens; the uroepithelial cells of these women have specific *E. coli*–binding glycolipids that are absent in secretors (33,77). Stapleton et al. (41) confirmed this association by demonstrating that nonsecretors are more susceptible than secretors to colonization with F-fimbriated *E. coli.*. However, in a recent report, Hopkins et al. (40) concluded that the overall risk for women to develop recurrent UTIs did not appear to be associated with any single HLA, ABO, or Lewis phenotype. An additional group that has frequent reinfections are postmenopausal women (43,57). The predominant factor in this group is the lack of estrogen, which leads to loss of lactobacilli and increased colonization of the vagina by *E. coli* (57).

Unlike patients with acute uncomplicated cystitis, patients with recurrent cystitis require a urine culture to document the presence of UTI (1). After confirmation by culture, recurrent cystitis can be managed depending on patient history with continuous or intermittent low-dose antimicrobial prophylaxis using one of three prophylactic strategies: (a) continuous prophylaxis, (b) post–coital prophylaxis, or (c) therapy initiated by patient for symptomatic recurrences (Fig. 15.4) (1). Relapse refers to recurrent infection caused by the original infecting uropathogens. Reinfection refers to recurrent infection with a different species or strain. Low-dose continuous prophylaxis for up to 5 years has been used successfully without emergence of antimicrobial resistance (124,125 and 126). Alternatively, patient-initiated therapy started when symptoms occur is convenient, safe, inexpensive, and effective (127). Suitable regimens include trimethoprim with or without sulfamethoxazole, nitrofurantoin, cephalexin, or quinolones (Table 15.11). Among postmenopausal women with recurrent cystitis, estrogen vaginal cream is a useful preventive measure with or without antimicrobial prophylaxis (43,125).

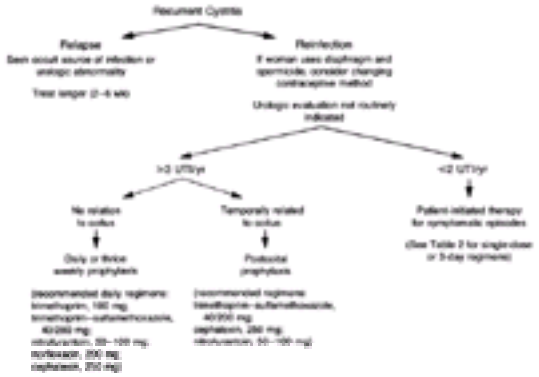


FIGURE 15.4. Strategies for managing recurrent cystitis in women.

1. Trimethoprim 100 mg
2. Trimethoprim-sulfamethoxazole 40/200 mg
3. Nitrofurantoin 50–100 mg
4. Norfloxacin 200 mg
5. Cephalexin 250 mg

TABLE 15.11. RECOMMENDED REGIMENS FOR ANTIMICROBIAL PROPHYLAXIS IN THE MANAGEMENT OF RECURRENT CYSTITIS

Acute Uncomplicated Pyelonephritis In Young Women

As in pregnancy, the clinical spectrum of acute uncomplicated pyelonephritis in nonpregnant young women ranges from a cystitis-like infection associated with mild flank pain to septicemia and septic shock (1). Similarly, treatment options have a wide range, from oral antimicrobial therapy for mild episodes to intravenous therapy for those with severe illness.

The major etiologic agent once again is *E. coli,* which is responsible for more than 80% of acute uncomplicated pyelonephritis cases in young women. As discussed in the section on pathogenesis, the uropathogenic strains of *E. coli* associated with acute pyelonephritis have specific determinants of virulence that allow them to infect the upper urinary tract (59,60,62,72,128). To summarize briefly, these uropathogenic strains of *E. coli* are members of the O : K : H serotype, produce aerobactin and hemolysin, and contain P fimbriae, which mediate attachment to uroepithelial cells

(1).

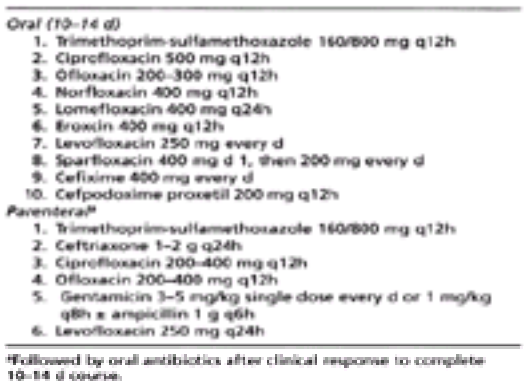
Clinical manifestations of acute pyelonephritis include symptoms of acute UTI (frequency, dysuria, urgency, and hematuria) in association with fever, chills, flank pain, and costovertebral angle tenderness. Nausea and vomiting may also be present. In the presence of these clinical findings, microscopic examination of urine (unspun) can help one make a presumptive diagnosis of acute pyelonephritis (Table 15.13). Pyuria is nearly always present and Gram-negative bacteria are usually present (1). The presence of white blood cell casts and red blood cells provides further evidence (1,7,129). In addition, the leukocyte esterase and nitrite dipstick test results are usually positive (129). However, as noted by Rubin et al. (130), nearly 20% of patients with acute pyelonephritis have urine cultures with less than 10^5 CFU/mL and thus will have a negative Gram stain of unspun urine. Unlike with acute uncomplicated cystitis, urine cultures should be obtained in all women with a presumptive diagnosis of acute pyelonephritis (1). Most authorities recommend that in the moderate to severe hospitalized cases of pyelonephritis, blood cultures should be obtained, as 15% to 20% are positive (130,131). Recently, the cost-effectiveness of routine blood cultures for young women even during pregnancy with acute pyelonephritis has been questioned (132). Because of the potential for severe, life-threatening sepsis in association with acute pyelonephritis, urine cultures remain indicated (117).

1. Structural abnormalities
2. Functional abnormalities
   - Unstable ("spastic") bladder
   - Atonic bladder
   - Outlet obstruction
   - Pelvic floor relaxation
3. Indwelling catheters
4. Postmenopausal women
5. Diabetes
6. Ederly patients
7. Urinary tract stones
8. Urologic surgery

TABLE 15.13. UNDERLYING CONDITIONS THAT PREDISPOSE TO COMPLICATED URINARY TRACT INFECTIONS

Increasing resistance to amoxicillin and first-generation cephalosporins has occurred, with 20% to 30% of organisms that cause pyelonephritis resistant to those agents (1,7,117,131). Thus, Stamm and Hooton (1) and the IDSA (117) recommend that these agents should no longer be used alone for empiric treatment of acute pyelonephritis. If mild disease is present in the absence of nausea and vomiting, ambulatory therapy with oral antibiotics is indicated (58,117,133). Those with moderate to severe illness or nausea and vomiting, as well as pregnant women, should be hospitalized for initial intravenous therapy. The regimens for treatment of acute pyelonephritis are listed in Table 15.12 In severe infections, parenteral therapy is continued until the patient becomes afebrile. This usually occurs within 48 to 72 hours (1). Oral therapy is then commenced, to complete a 14-day course of

treatment. In patients whose fever and flank pain persist for more than 72 hours, the urine culture should be repeated and the presence of a perinephric or intrarenal abscess, urologic abnormalities, or obstruction should be sought using ultrasonography or computed tomography (CT) (1). Unlike with acute cystitis, with pyelonephritis, test of cure cultures should be obtained at 2 weeks after completion of treatment (1).



Oral (10–14 d)

1. Trimethoprim-sulfamethoxazole 160/800 mg q12h
2. Ciprofloxacin 500 mg q12h
3. Ofloxacin 200–300 mg q12h
4. Norfloxacin 400 mg q12h
5. Lomefloxacin 400 mg q24h
6. Enoxin 400 mg q12h
7. Levofloxacin 250 mg every d
8. Sparfloxacin 400 mg d 1, then 200 mg every d
9. Cefixime 400 mg every d
10. Cefpodoxime proxetil 200 mg q12h

Parenteral[a]

1. Trimethoprim-sulfamethoxazole 160/800 mg q12h
2. Ceftriaxone 1–2 g q24h
3. Ciprofloxacin 200–400 mg q12h
4. Ofloxacin 200–400 mg q12h
5. Gentamicin 3–5 mg/kg single dose every d or 1 mg/kg q8h + ampicillin 1 g q6h
6. Levofloxacin 250 mg q24h

[a]Followed by oral antibiotics after clinical response to complete 10–14 d course.

TABLE 15.12. RECOMMENDED REGIMENS FOR THE TREATMENT OF ACUTE UNCOMPLICATED PYELONEPHRITIS IN NONPREGNANT YOUNG WOMEN

For many years, the traditional approach for management of patients with acute pyelonephritis was hospitalization and treatment with antimicrobial agents for up to 6 weeks (117). Subsequently, studies demonstrated that a 2-week course of therapy provided satisfactory outcome in most young healthy women with acute pyelonephritis (134,135). More recently, studies have demonstrated that 5 to 7 days of antimicrobial therapy for acute pyelonephritis is adequate, particularly in patients with mild to moderate infection (120,136,137). In addition, multiple studies demonstrated that intravenous antimicrobial agents may not be necessary for all, perhaps none, of the therapy (117,120,134,135,138,139). Although some authors (46) advocate outpatient therapy for pregnant women with acute pyelonephritis, Hooton and Stamm (7) recommend that, in general, outpatient therapy should be reserved for nonpregnant women with mild to moderate uncomplicated pyelonephritis, who are complaining, can be easily reached by telephone, and are likely to return in a timely manner if symptoms do not respond rapidly to oral therapy.

Hooton and Stamm (7) recommend that in the absence of suspicion for Gram-positive organisms on Gram stain (e.g., enterococci or group B streptococci), empiric therapy for hospitalized patients with acute uncomplicated pyelonephritis with ceftriaxone (1 g per 24 hours) should be initiated. Aminoglycosides given once daily are also effective and safe (7). Similarly ciprofloxacin and ofloxacin have been shown to be effective for the parenteral treatment of uncomplicated pyelonephritis. Other appropriate agents include penicillin–b-lactamase inhibitor combinations (e.g., ampicillin-sulbactam, ticarcillin–clavulanic acid, piperacillin-tazobactam). If enterococci are suspected, ampicillin-gentamicin or a penicillin–b-lactamase inhibitor is a good choice (7). In areas with increasing resistance to trimethoprim-sulfamethoxazole, this agent should not be used for empiric therapy of

pyelonephritis (7). In general, oral therapy can be commenced after 24 to 48 hours of parenteral treatment.

For oral empiric therapy of acute uncomplicated pyelonephritis with Gram-negative bacteria (based on Gram stain), Hooton and Stamm (7) recommend the use of a fluoroquinolone. Trimethoprim-sulfamethoxazole is an alternative agent for initial empiric therapy in geographic areas where uropathogens associated with acute pyelonephritis remain susceptible (7,117). If enterococci are suspected, amoxicillin is added to a fluoroquinolone (7). New broad-spectrum cephalosporins (e.g., cefixime and cefpodoxime proxetil) are also effective for the treatment of acute uncomplicated pyelonephritis. However, Hooton and Stamm (7) caution that cefixime is not effective against *S. saprophyticus.*

Recently the IDSA published guidelines for antimicrobial treatment of uncomplicated pyelonephritis in women (117). They concurred that for young nonpregnant women with normal urinary tracts, 14 days of antimicrobial therapy is sufficient (A, I). In mild or moderate cases, a 7-day course with highly active agents may be adequate (B, I). The IDSA suggests that mild cases of uncomplicated acute pyelonephritis can be managed with oral antimicrobial agents (A, II) and recommends an oral fluoroquinolone (A, II), or if the organism is known to be susceptible, trimethoprim-sulfamethoxazole (B, II). If Gram-positive bacteria are suspected, amoxicillin or amoxicillin–clavulanic acid may be used alone (B, III). Hospitalization is recommended for more severe cases of acute pyelonephritis (A, II), which are treated with parenteral fluoroquinolones, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside (B, III). For Gram-positive cocci in severe cases, the IDSA recommends ampicillin-sulbactam with or without an aminoglycoside (B, III). Once the patient improves, the regimen can be switched to an oral agent to which the causative organism is sensitive (117).

Complicated Urinary Tract Infection

As defined by Stamm and Hooton (1), complicated UTIs are those that occur in patients with a functionally, metabolically, or anatomically abnormal urinary tract or that are caused by pathogens that are resistant to antibiotics. Table 15.13 lists the underlying conditions that predispose to complicated UTI. Ronald and Harding (140) recently proposed a classification of complicated UTIs (Table 15.14). Complicated UTIs encompass the entire spectrum of UTIs including ASB, mild cystitis, pyelonephritis, or urosepsis. As shown in Fig. 15.5 and Table 15.15, a broader range of bacteria is associated with complicated UTIs, compared with that responsible for acute uncomplicated cystitis (1,7,140). Because many of these bacteria are resistant to multiple antimicrobial agents, it is critical that urine cultures be obtained and susceptibility testing accomplished in these patients (1,7). Stamm and Hooton (1) recommended that for empiric therapy for patients with mild to moderate infection who can be treated with oral medication on an ambulatory basis, the fluoroquinolones should be used (Table 15.16). These agents provide a broad spectrum of antimicrobial activity, covering most pathogens associated with complicated UTI, and achieve high levels both in urine and in urinary tract tissue. When the pathogen has been identified and is susceptible, trimethoprim-sulfamethoxazole is a reasonable and less expensive choice for treatment (1). When dealing with more severe complicated UTIs requiring hospitalization, one can prescribe various parenteral agents (Table 15.17). For initial

empiric therapy of the seriously ill, hospitalized patient with complicated UTI, ampicillin-gentamicin or imipenem-cilastatin provides coverage against almost all potential pathogens including *Pseudomonas aeruginosa* and most enterococci (1). Once culture results are available, therapy can be modified. For complicated UTIs, a 10- to 14-day course of therapy is necessary. Most patients who commence therapy parenterally can be switched to oral treatment based on susceptibility reports once clinical response is apparent. Some authorities recommend a longer duration of therapy for complicated UTIs due to *Pseudomonas* or *Enterococcus* because these infections are difficult to treat (1). A urine culture should be obtained 1 to 2 weeks posttreatment. Frequent recurrences should lead to studies assessing potential underlying anatomic, functional, or metabolic defects (1).

Structural abnormalities
Obstruction
Prostatic infection
Calculi
Urinary diversion procedures
Infected cysts
External drainage (catheters, nephrostomy tubes)
Stents
Vesicoureteral reflux
Neurogenic bladder
Bladder or renal abscesses
Fistulae
Metabolic/hormonal abnormalities
Diabetes mellitus
Pregnancy
Renal impairment
Xanthogranulomatous pyelonephritis
Malacoplakia
Primary biliary cirrhosis
Impaired host responses
Transplant recipients
Neutropenia
Congenital vs. acquired immunodeficiency syndromes
Unusual pathogens
Yeasts and fungi
Mycoplasmata
Resistant bacteria including *Pseudomonas aeruginosa*
Calculi predisposing bacteria (*Proteus* sp and *Corynebacterium ureafyticum*)

Source: From Ronald AR, Harding GKM. Complicated urinary tract infections. Infect Dis Clin North Am 1992;11:583–592, with permission.

TABLE 15.14. COMPLICATED URINARY TRACT INFECTION CLASSIFICATION

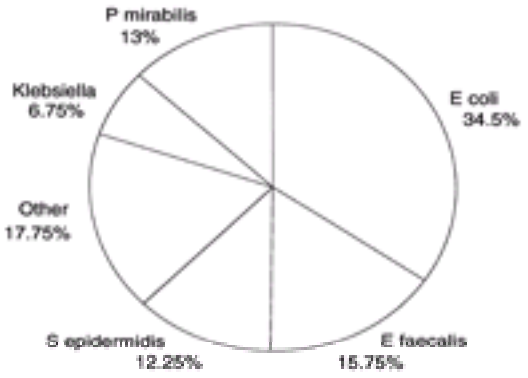


FIGURE 15.5. Pathogens responsible for complicated urinary tract infections.

Pathogen	%	Pathogen	%
Pseudomonas	5	*Acinetobacter*	1.5
Staphylococcus aureus	4	*Citrobacter*	1
Enterobacter	2.5	*Providencia*	0.25
Serratia	1.5	*Morganella morganii*	0.25
Streptococci	1.5	*Candida*	0.25

TABLE 15.15. OTHER PATHOGENS RESPONSIBLE FOR COMPLICATED URINARY TRACT INFECTIONS

1. Ciprofloxacin 500 mg q12h
2. Enoxacin 400 mg q12h
3. Lomefloxacin 400 mg q24h
4. Ofloxacin 200 mg q12h
5. Norfloxacin 400 mg q12h
6. Levofloxacin 250 mg q24h
7. Sparfloxacin 400 mg/day 1, then 200 mg q24h

[a]Oral therapy for 10–14 d.

TABLE 15.16. TREATMENT OF MILD-TO-MODERATE COMPLICATED URINARY TRACT INFECTION IN WOMEN WITHOUT NAUSEA AND VOMITING[a]

1. Ampicillin 1 g q6h and gentamicin 3–5 mg/kg as single dose or 1 mg/kg q8h
2. Imipenem-cilastatin 250–500 mg q6–8h
3. Ciprofloxacin 200–400 mg q12h
4. Ofloxacin 200–400 mg q12h
5. Ceftriaxone 1–2 g q24h
6. Aztreonam 1 g q8–12h
7. Ticarcillin-clavulanate 3.2 g q8h
8. Levofloxacin 250 mg q24h

[a]Continue parenteral therapy until afebrile and then switch to oral therapy to complete a 14–21-d course of treatment.

TABLE 15.17. TREATMENT OF SEVERE COMPLICATED URINARY TRACT INFECTIONS IN WOMEN REQUIRING HOSPITALIZATION[a]

Asymptomatic Bacteriuria

The diagnostic criterion for ASB is more than or equal to 10^5 CFU/mL on two successive urine cultures (1,12). Among adults, routine screening for ASB is only indicated before urologic surgery and during pregnancy (1). Management of ASB in pregnancy is discussed in a later section of this chapter. Detection and treatment of bacteriuria before urologic surgery reduces the risk for postoperative UTIs including sepsis (1,141). Although ASB occurs in up to 40% of older adult men and women (older than 65 years), particularly those in nursing homes, routine screening for and treatment of ASB are not recommended because complications such as pyelonephritis and sepsis are rare (1). Treatment can be based on the results of susceptibility testing.

Using the definition of more than or equal to 10^5 CFU/mL, the prevalence of ASB in healthy women aged 18 to 40 years is generally 5% (142). Although ASB is common and associated with adverse outcomes in pregnant women (143,144,145 and 146) and patients undergoing urologic procedures (1,141), little information is available that elucidates its risk factors, pathogenesis, natural history, or temporal relationship to symptomatic UTI in healthy young women (142). Hooton et al. (142) recently reported the results of a prospective evaluation of nearly 800 sexually active women aged 18 to 40 years followed over a 6-month period. The prevalence of ASB was 5% and 6% in a university health service and HMO, respectively. Persistent ASB with the same strain of *E. coli* was rare. Symptomatic UTI occurred within 1 week in 8% of occasions in which ASB was detected, compared with 1% when cultures were negative ($P < 0.001$). By multivariate analysis, recent use of a diaphragm plus spermicide and recent sexual intercourse were strongly associated with ASB. Persistent bacteriuria (i.e., that lasting at least 2 months) was very uncommon (less than 1% of women). Thus, the authors concluded that ASB is common in young women but rarely persists (142). In addition, ASB is a strong predictor of subsequent symptomatic UTI (142). Interestingly, the risk factors for asymptomatic and symptomatic UTI are the same (143). As noted by Nicolle (143), the intriguing question raised by the study by Hooton et al. (142) is why some women who are at increased risk for UTI develop asymptomatic and others develop symptomatic disease. Because the genotypes of *E. coli* were similar in asymptomatic and symptomatic UTI, Nicolle (143) suggested that development of symptomatic infection may result from a complex interaction between phenotypic expression of virulence factors and variation in the host environment.

URINARY TRACT INFECTION IN PREGNANCY

Epidemiology

UTI is the most common medical complication of pregnancy, either asymptomatic (ASB of pregnancy) or symptomatic (cystitis or acute pyelonephritis). Although most UTIs in pregnancy are asymptomatic (144), covert bacteriuria increases the risk of preterm birth and low-birthweight infants (145,146 and 147).

In the mid-1950s, the investigative work of Kass documented that significant bacteriuria can occur in the absence of symptoms or signs of UTIs (1). Kass (13,148)

identified persistent ASB in 6% of prenatal patients. Acute pyelonephritis developed in 40% of these patients receiving a placebo; when bacteriuria was eliminated, pyelonephritis did not occur. He noted that neonatal death rates and prematurity rates were two or three times greater in bacteriuric women receiving placebo than in nonbacteriuric women or bacteriuric patients in whom bacteriuria was eliminated (149,150). He concluded that detection of maternal bacteriuria would identify a group of patients at risk for pyelonephritis and premature delivery, and that pyelonephritis could be prevented by detection and treatment of bacteriuria in early pregnancy. Moreover, with treatment of bacteriuria, 5% to 10% of premature deliveries could be prevented.

It has long been recognized that symptomatic UTI is more frequently encountered in pregnant women. This suggests that factors are present during gestation that allow bacteria to replicate in the urine and ascend to the upper urinary tract. Several findings support this view. The normal female urinary tract undergoes dramatic physiologic changes during pregnancy (8,144). There is decreased ureteric muscle tone and activity, which results in a reduced rate of passage of urine throughout the urinary collecting system. The upper ureter and renal pelvises become dilated, resulting in a physiologic hydronephrosis of pregnancy. This hydronephrosis is a result of the effects of progesterone on muscle tone and peristalsis, and most importantly, mechanical obstruction by the enlarging uterus. Bladder changes also occur in pregnancy, including decreased tone, increased capacity, and incomplete emptying. These findings predispose to vesicoureteric reflux. These physiologic alterations associated with pregnancy facilitate the ascending migration of bacteria into the upper urinary tract once bladder infection is established.

It is also possible that alterations in the physical or chemical properties of urine during pregnancy can result in exacerbations of bacteriuria, thus predisposing to ascending infection. Urinary pH elevation during pregnancy encourages bacterial growth. Glycosuria, which is common in pregnancy, may favor an increase in the rate of bacterial multiplication. The increased urinary excretion of estrogen may be a factor in the pathogenesis of symptomatic UTI during pregnancy. It has been demonstrated by means of animal experiments that estrogen can enhance the growth of strains of *E. coli* that cause pyelonephritis and also predispose the animal to the development of renal infection (151,152). In addition, the renal medulla is particularly susceptible to infection because its hypertonic environment inhibits leukocyte migration, phagocytosis, and complement activity (152,153 and 154).

The cumulative effect of these physiologic factors is an increased risk for ascending infection from the bladder, colonized with bacteria, to the kidneys. The bulk of investigations have shown that most patients with ASB of pregnancy will be detected at the initial prenatal visit and that relatively few pregnant women acquire bacteriuria after the initial visit (1,13,144,155). There is no evidence that bacteriuria is acquired between the time of conception and the first antenatal visit. There is sufficient evidence that in many instances, the bacteriuria antedates the pregnancy. Several investigations have shown that nonpregnant populations had an incidence of ASB comparable to that found in pregnant women in the same locale. It appears that the major source of patients with bacteriuria first discovered during pregnancy are those women who acquired ASB early in life and in whom the incidence of bacteriuria increased as a result of sexual activity. Although pregnancy per se does not cause any major increase in bacteriuria, it does predispose to the development of acute pyelonephritis in these patients (8,144,155). Rates for pyelonephritis in indigent

pregnant women not screened for ASB have ranged from 4% to 6% (156).

Asymptomatic Bacteriuria

As a result of Kass's initial observations, considerable interest has focused on ASB in pregnant women (13). The prevalence of ASB in pregnant women ranges from 2% to 11% (Table 15.18), with most investigations reporting an incidence between 4% and 7% (13,155,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189 and 190). The incidence of ASB is to a great extent dependent on socioeconomic factors, with infections being five times more common in indigent women. Similarly, the risk is doubled in women with sickle cell trait (191). Diabetes increases the risk of bacteriuria and is associated with organisms other than *E. coli* such as *Klebsiella* and *Proteus* (192). As reported by Stamm et al. (193), prior UTI is associated with an increased risk of ASB in pregnancy.

Study	Total No. of Patients	No. of Patients with Bacteriuria	% Bacteriuria
Wilson et al. (181)	6,216	137	2.2
Blunt and Williams (165)	1,055	27	2.5
Wren (180)	3,099	90	2.9
Grunebaum et al. (158)	8,937	392	3.5
Stuart et al. (163)	2,713	95	3.5
Pathak et al. (169)	7,632	288	3.8
Williams et al. (164)	5,542	211	3.8
Gower et al. (167)	5,000	265	4.4
Kacho and Holder (174)	616	27	4.4
Cindle et al. (158)	4,590	210	4.6
Dixon and Brandt (180)	1,380	71	5.14
Little (168)	5,000	265	5.3
Eykin and McFadyen (173)	5,000	59	5.9
Kincaid-Smith (175)	4,000	240	6.0
Robertson et al. (178)	8,271	511	6.2
Carrol et al. (166)	5,200	335	6.4
Singh et al. (176)	1,684	111	6.4
LeBlanc and McGanity (168)	1,325	87	6.5
Norden and Kjaderick (162)	1,788	111	6.5
McFadyen et al. (161)	2,000	132	6.6
Layton (177)	1,000	67	6.7
Savage et al. (177)	6,232	431	6.9
Turner (172)	1,500	108	7.0
Bryant et al. (157)	448	32	7.1
Monson et al. (179)	1,400	102	7.3
Patrick (179)	2,521	219	8.7

TABLE 15.18. PREVALENCE OF BACTERIURIA IN PREGNANCY

It is generally accepted that untreated ASB during pregnancy often leads to acute pyelonephritis in 20% to 30% of cases (144). For this reason, it is clear that bacteriuria must be viewed with concern. However, other claims—such as those that say ASB predisposes the patient to anemia (170,177,187,188), hypertension or preeclampsia (162,163,180,184,188,180), chronic renal disease, amnionitis (189), and endometritis (190)—are controversial and unproved. Until recently, the association between bacteriuria and prematurity and low-birthweight infants was even more controversial. However, recent analysis supports an association between ASB and preterm birth and low birthweight (145,146 and 147). As a result of the risks for acute pyelonephritis and preterm delivery and low birthweight, the American College of Obstetricians and Gynecologists, the U.S. Preventive Services Task Force, and the Canadian Task Force on the Periodic Health Examination recommend screening to detect ASB in pregnancy (194,195 and 196).

As in nonpregnant women, *E. coli* has been the predominant pathogen isolated in each study of ASB in pregnant women and was present in 60% to 90% of the cases. The next most common are *Proteus mirabilis, Klebsiella pneumoniae,* and

Enterococcus. Group B b-hemolytic streptococci are also recognized as potential pathogens in the urinary tract during pregnancy (197). Recently, *S. saprophyticus* has been noted to be an important pathogen in UTIs among women (44,45).

Bacteriuria And Pyelonephritis

Acute pyelonephritis, one of the most frequent medical complications of pregnancy, is a serious threat to maternal and fetal well-being (93,198). The association between acute pyelonephritis of pregnancy and preterm delivery was appreciated in the preantibiotic era, with prematurity rates of 20% to 50% being reported (199,200,201 and 202). Subsequent studies in the postantibiotic era have confirmed this association between acute pyelonephritis and an increased risk of premature delivery (3,13,18,21,22,162,203,204,205,206 and 207). More recently, Millar and Cox (93) noted that the contribution of pyelonephritis to preterm birth and low birthweight is confounded by socioeconomic status, which is closely related to both prematurity and UTI and thus difficult to ascertain. However, they concluded that the weight of evidence demonstrates that pyelonephritis is associated with preterm birth and low birthweight, but the strength of the association is unknown (93).

In the past, several mechanisms have been proposed to explain this association, including (a) pyrogens increase myometrial activity (208); (b) ureteric contractions result in reflex myometrial contractions (199); (c) endotoxin of Gram-negative bacteria associated with pyelonephritis has a direct oxytocic effect on the myometrium (205,209); or (d) endotoxin crosses the placenta, resulting in fetal effects culminating in preterm labor. Newer theories suggest that bacterial enzymes such as proteases and collagenase may weaken membranes, predisposing them to rupture and initiating the onset of labor (210). In addition, bacterial products such as phospholipase A and C or endotoxins may stimulate synthesis of prostaglandins from the membranes or decidua, which initiates labor (211). More importantly, these bacterial products stimulate the monocytes and macrophages of the immune system to release cytokines such as IL-1, IL-6, tumor necrosis factor, and platelet activating factor, which in turn trigger prostaglandin production (209).

The concept of quantitative urine cultures, which made it possible to determine when infection of the urinary tract was present in individuals without symptoms or signs of UTI, was a major contribution to the understanding of the pathogenesis of pyelonephritis. Kass's initial studies determined that the presence of ASB was the most significant factor associated with the development of acute pyelonephritis in pregnancy (12,13). Kass noted that 20% to 40% of pregnant women with ASB receiving a placebo developed pyelonephritis subsequently during the pregnancy. However, when the bacteriuria was treated and eliminated with antimicrobial agents, pyelonephritis did not occur. Subsequent studies have confirmed that detection of ASB in pregnant women does identify a group of patients at high risk to develop acute pyelonephritis during pregnancy (Table 15.19). In these studies, 13.5% to 65% of pregnant women with ASB who were not treated subsequently developed acute pyelonephritis during pregnancy (18,157,160,162,168,169,173,174,175,176,177 and 178,182,184,210). Detection and treatment of pregnant women with ASB significantly reduces the risk of developing pyelonephritis (Table 15.19). Initially Kass maintained that pyelonephritis, with its attendant maternal and fetal morbidity and mortality, could be completely prevented by detecting and treating bacteriuria early in pregnancy (12,13). In contrast, most investigators have found that a small proportion of women without bacteriuria at the first antenatal visit will develop pyelonephritis.

The explanation for this phenomenon is that approximately 1% of pregnant women who do not have bacteriuria at the first antenatal visit acquire ASB later in pregnancy. These women are then at risk for developing pyelonephritis. In pregnant women whose bacteriuria was treated, the reported incidence of pyelonephritis ranged from 0% to 5.3%, with an average of 2.9%. In addition, few women with bacteriuria will develop pyelonephritis before their first prenatal visit. Although detection and eradication by treatment of bacteriuria early in pregnancy will not completely eliminate pyelonephritis, it should prevent at least 70% to 80% of the cases of pyelonephritis in pregnancy.

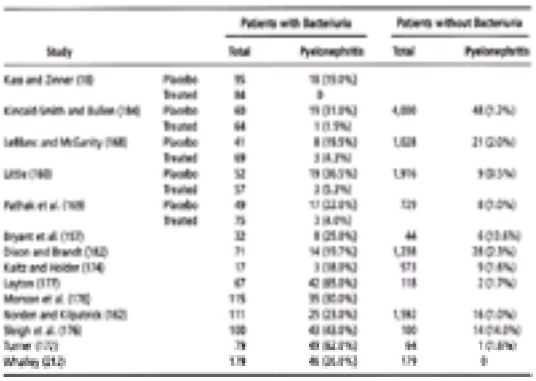


TABLE 15.19. RELATIONSHIP BETWEEN ASYMPTOMATIC BACTERIURIA AND PYELONEPHRITIS IN PREGNANCY

Widespread screening for ASB in pregnancy has significantly reduced the incidence of pyelonephritis in pregnancy over the past two decades (213,214 and 215). Harris (213) demonstrated that initiation of routine screening for and treatment of ASB in pregnant women resulted in a decreased incidence of pyelonephritis, from 4% to 0.8%. Similarly, in Barcelona, Gratacos et al. (214) noted a significant reduction in the incidence of pyelonephritis, from 1.8% to 0.6% ($p < 0.001$) after the introduction of a program to screen for and treat ASB in pregnancy. Wadland and Plante (94) noted that screening for ASB in pregnancy was cost-effective when the prevalence of bacteriuria was more than 2%. More recently, Rouse et al. (95) performed a cost-effectiveness and cost-benefit analysis and concluded that screening for and treating ASB to prevent pyelonephritis in pregnancy is cost beneficial. In their analysis, no screening resulted in 232 cases of pyelonephritis per 1,000 pregnancies, compared with 16.2 cases with dipstick (leukocyte esterase nitrite) screening and 11.2 with culture screening. Although culture screening prevented one third more cases of pyelonephritis, it cost nearly $3,500 for each additional case prevented and was not cost beneficial, compared with dipstick screening (95).

Multiple studies have attempted to identify those pregnant patients with bacteriuria who are at the greatest risk for developing acute pyelonephritis. As noted already, localization of UTI has been attempted using various methodologies. The results of these investigations suggest that renal involvement already exists in many pregnant women with bacteriuria, despite lack of clinical evidence for upper urinary tract or kidney infections. Based on these attempts to localize the site of asymptomatic UTI,

it has been suggested that 25% to 50% of pregnant women with ASB have renal tissue involvement and silent pyelonephritis (183,209,216,217). The bacteriuric women with subclinical renal involvement are at high risk to develop symptomatic pyelonephritis during pregnancy.

Bacteriuria And Anemia

Several studies have noted an association between bacteriuria in pregnant women and the presence of anemia (170,177,186,218). However, other studies have failed to document such an association (155,158,160,171,174).

It is difficult to reconcile these opposing views and results. It seems reasonable that those bacteriuric women with subclinical renal disease would have a greater risk of developing anemia. However, with the use of antibody-coated bacteria, Gilstrap et al. (219) failed to demonstrate this association. The relation between bacteriuria and low socioeconomic status might explain the propensity for anemia to be more prevalent in pregnant women with bacteriuria. Socioeconomic deprivation, bacteriuria, and anemia are features common to patients going to prenatal clinics. Thus, any causal relationship between bacteriuria and anemia remains to be documented.

Bacteriuria And Hypertension

An increased incidence of hypertensive disease of pregnancy has been alleged to exist in pregnant women with ASB. Although some investigations have confirmed this postulate (161,162,169,175,184), in general, most workers have failed to document any association between bacteriuria and hypertension (157,158,160,168,171,187). Moreover, the studies supporting an association between bacteriuria and gestational hypertension have reported conflicting results about whether eradication of bacteriuria by antimicrobial treatment reduces the incidence of hypertensive disease of pregnancy among bacteriuric women (150,160,168,169 and 170,184). Today, an association between bacteriuria and hypertensive disease of pregnancy is questionable.

Bacteriuria And Chronic Renal Disease

Zinner and Kass (220) estimated that 10% to 15% of bacteriuric pregnant women are destined to have evidence of chronic pyelonephritis 10 to 12 years after delivery, and that renal failure will ultimately develop in 1 of 3,000 pregnant women with bacteriuria (18). Several groups of investigators have reported that women with bacteriuria who were not treated during pregnancy have persistent bacteriuria over the year postdelivery in 35% to 80% of cases (178,187,220,221 and 222). Other groups have noted that bacteriuria still persisted in 20% to 30% of patients, even when the bacteriuria had been treated during pregnancy (18,167,175,220). Zinner and Kass (220) reported that 20% of women with bacteriuria during pregnancy had persistent bacteriuria at follow-up examination 10 to 12 years postdelivery. In contrast, only 5% of women who were not bacteriuric during pregnancy had significant bacteriuria at the 10- to 12-year follow-up examination. The rate of bacteriuria was similar whether the patient had been treated or received a placebo. It has been suggested that the patients with evidence of underlying renal involvement are the group at high risk to have persistent bacteriuria after delivery. Studies of antibody-coated bacteria have

demonstrated that one half of ASB cases are renal in origin (223).

Follow-up investigations with intravenous pyelography have disclosed that women with pregnancy bacteriuria have an 8% to 33% incidence of radiologic changes consistent with pyelonephritis (158,161,167,169,178,184,187,220,221 and 222). In addition, these authors have found a high incidence of other abnormalities, such as congenital anomalies of the urinary tract, renal calculi, and ureteric dilatation. The highest incidence of radiologic evidence of chronic pyelonephritis was noted in those patients who had infection localized in the upper urinary tract or in whom bacteriuria during pregnancy was difficult to eradicate.

Because of the incidence of persistent bacteriuria, abnormal renal function, and radiologic evidence of chronic pyelonephritis, which has been documented in follow-up studies of patients with ASB of pregnancy, long-term follow-up of mothers with bacteriuria is essential. They should be closely followed with periodic urine cultures and treatment if bacteriuria persists or recurs. Patients with relapses and ASB that is difficult to eradicate should undergo (after pregnancy) intravenous pyelograms to detect urinary tract abnormalities that may be correctable or chronic pyelonephritis. With such close surveillance and management, the progression to end-stage renal disease may hopefully be delayed or prevented.

Bacteriuria And Preterm Delivery And Low-Birthweight Infants

It is well documented that pregnant women who develop acute pyelonephritis are at a significantly increased risk for preterm labor and delivery. In contrast, the relationship of ASB to preterm delivery, low-birthweight, small for gestational age babies, and fetal mortality has been controversial. Kass and Finland (12), Kass and Zinner (18), and Elder et al. (150) initially reported that there was an association between ASB and prematurity, and that eradication of bacteriuria with antimicrobial therapy significantly reduced the rate of premature delivery. Kass noted that the prematurity rate was two to three times greater in bacteriuric women receiving a placebo than in nonbacteriuric women or patients whose bacteriuria had been eliminated. Kass initially suggested that early detection and treatment of bacteriuria would prevent 10% to 20% of prematurities. The term “prematurity” in the initial study was based entirely on a birthweight of 25,000 g or less.

Since Kass's initial studies, numerous studies have concerned themselves with the role ASB plays in the development of preterm labor and delivery or low-birthweight infants (Table 15.20). Although many workers have confirmed the original finding by Kass (158,163,168,169,170 and 171,177,184,186,187,205), many other investigators have failed to confirm a relationship between ASB and preterm delivery or low-birthweight infants (22,155,157,160,162,168,174,178,212,223). Leveno et al. (223) were also unable to document an influence on the incidence of preterm delivery or low-birthweight infants in the subgroup of women with ASB with evidence of renal infection based an antibody-coated bacteria. In controlled trials in which treatment of bacteriuria was compared with placebo, the results are also conflicting (Table 15.21). Although some workers noted that antibiotic treatment of bacteriuria did not significantly reduce the rate of occurrence of low-birthweight infants (160,184), others have reported a significant reduction in the incidence of premature births when bacteriuria was eradicated with antimicrobial therapy (148,168,169,170 and 171,187,205).

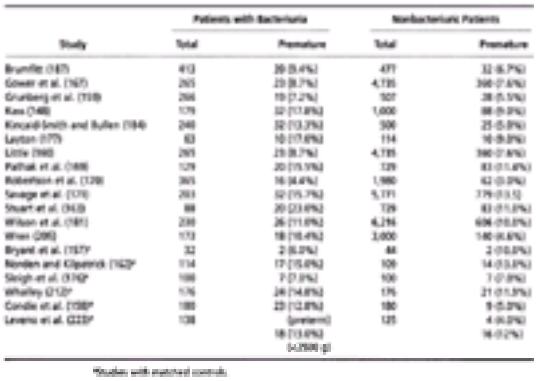


TABLE 15.20. BACTERIURIA AND PREMATURITY

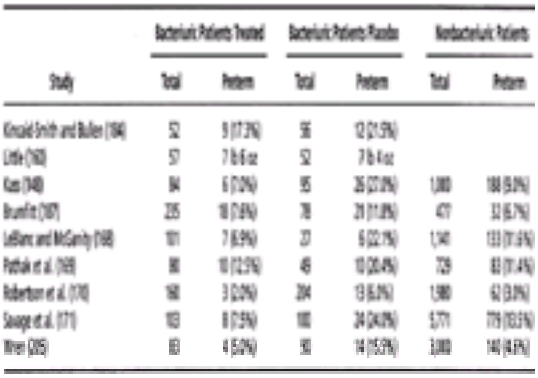


TABLE 15.21. EFFECT OF TREATMENT FOR BACTERIURIA ON PRETERM DELIVERY

Kincaid-Smith and Bullen (184) were the first to suggest that underlying renal disease was the major risk factor for the excess prematurity or low birthweight among the infants of the bacteriuric women. Gruneberg et al. (159) noted that an increased rate of prematurity and a decrease in infants' birthweight occurred in those bacteriuric women who either were refractory to treatment or in whom bacteriuria had recurred. Previous investigations had reported that bacteriuric patients who do not respond to treatment are likely to have subclinical renal involvement (100,224). These data have been used to support the hypothesis that those women with subclinical renal involvement are the population at risk to deliver preterm or low-birthweight infants. The varying definitions for prematurity used in the literature have contributed to the confusion that exists. Unfortunately, most of the studies have used a definition of prematurity based on a weight of less than 2500 g, rather than infants delivered at less than 37 weeks of gestation. Thus, the relationship between bacteriuria and preterm and low-birthweight and small for gestational age infants was debated. Many variables comprise the etiology of prematurity, and bacteriuria is only one of the many factors that may influence the onset of premature labor (145). As

the incidence of both pregnancy bacteriuria and prematurity increases with decreasing socioeconomic status, any relationship between bacteriuria and gestational length and birthweight may be complex and difficult to establish.

Romero et al. (146) applied metaanalysis methodology in an analysis of the relationship between ASB and preterm delivery and low birthweight. These authors analyzed cohort studies of ASB during pregnancy and randomized treatment control trials of ASB. In the cohort studies, nonbacteriuric women had two thirds the risk for low birthweight (relative risk, 0.65; 95% CI, 0.57–0.74) and one half the risk for preterm delivery (relative risk, 0.50; 95% CI, 0.36–0.70) as untreated pregnant women with ASB (Table 15.22). Moreover, antibiotic treatment significantly reduced the risk of low birthweight (Table 15.23). Romero et al. (146) concluded that clinical and epidemiologic evidence demonstrates a strong association between untreated ASB and low birthweight or preterm delivery, and that antibiotic treatment of ASB is effective in reducing the occurrence of low birthweight. Subsequently, Schieve et al. (147) assessed the risk for low-birthweight, premature infants, preterm infants, and small for gestational age births in a retrospective cohort analysis of more than 150,000 births in the University of Illinois Perinatal Network database. Women exposed to antepartum UTI were at greater risk of delivering infants with low birthweight, premature infants, preterm infants, and infants who were small for their gestational age. Although multivariate analysis reduced the risk, estimates all remained statistically significant, except the “small for gestational age” association. The ORs for low birthweight (1.4; 95% CI, 1.2–1.6), preterm birth (1.3; 95% CI, 1.1–1.4), and preterm and low birthweight (1.5; 95% CI, 1.2–1.7) were similar to those reported in the metaanalysis by Romero et al. (146) (relative risks, 1.5 and 2.0 for low birthweight and preterm delivery, respectively).

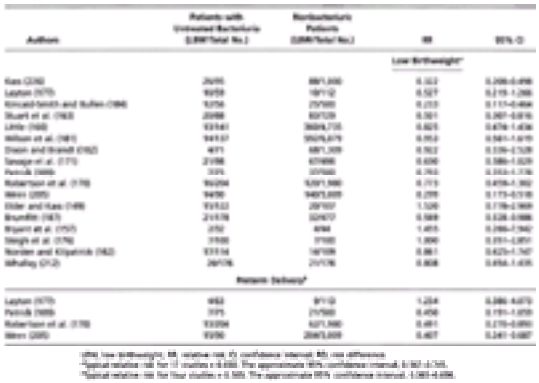


TABLE 15.22. METAANALYSIS OF THE INCIDENCE OF LOW BIRTHWEIGHT OR PRETERM DELIVERY IN PATIENTS WITH OR WITHOUT BACTERIURIA: COHORT STUDIES[a]

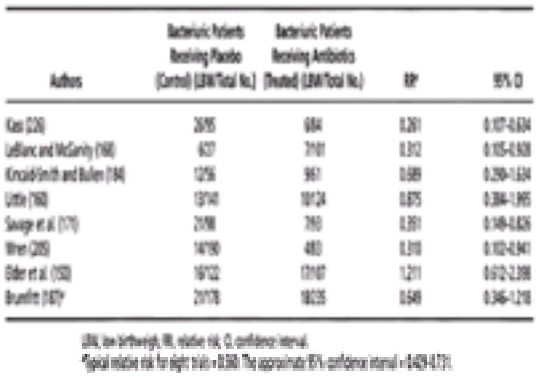


TABLE 15.23. METAANALYSIS OF THE INCIDENCE OF LOW BIRTHWEIGHT IN PATIENTS WITH BACTERIURIA: RANDOMIZED CLINICAL TRIALS

Bacteriuria And Fetal Loss, Fetal Infection, And Congenital Anomalies

An increased frequency of abortions and stillbirths in pregnant women with bacteriuria has been reported by some investigators (158,177,184,187,205), but not confirmed by others (173,179). In addition, some reports demonstrated a significant decrease in the incidence of spontaneous abortions and stillbirths when bacteriuria was successfully eradicated with antimicrobial therapy (159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204 and 205), whereas others failed to show a significant difference in the abortion and stillbirth rates between treated and untreated women with bacteriuria (184).

An association between maternal bacteriuria and congenital abnormalities has also been proposed. Patrick (179) noted an increased incidence of dorsal midline fusion defects in the offspring of women with ASB. Savage et al. (171) and Kincaid-Smith and Bullen (184) also noted an increase in congenital abnormalities in the newborns of bacteriuric women. However, establishment of a causal relationship between bacteriuria of pregnancy and congenital anomalies must await further investigations.

Diagnosis of Asymptomatic Bacteriuria In Pregnancy

Although the diagnosis of ASB was originally based on two consecutive midstream urine cultures containing >100,000 CFUs/mL of a single uropathogen, clinically only a single urine specimen is obtained due to the expense of using two cultures as a screening test (93). Two successive positive urine cultures detect approximately 95% of the cases of ASB, which approaches the accuracy of catheterization (148,225,226). Use of a single positive culture detects 80% of ASB cases. Obtaining a good specimen for urine culture requires careful instruction to the patient to minimize contamination from the vagina, distal urethra, and labia. The midstream urine specimen should be obtained after the external genitalia is washed two or three times with a cleansing solution, from vagina toward anus. Ideally a urine culture specimen should be processed immediately, because at room temperature, bacteria

will begin to multiply, yielding a false-positive result. Alternatively, urine specimens can be refrigerated for up to 24 hours before transport to the laboratory without affecting the result.

Because cultures are relatively expensive and require 24 to 48 hours for results, inexpensive, rapid, office-based screening tests have been introduced into clinical practice (93). However, the most accurate method for detecting ASB in pregnancy remains culture (93). In addition, Rouse et al. (95) recently demonstrated that culture screening would prevent one third more cases of pyelonephritis than dipstick screening, although at a greater cost per case prevented. Microscopic urinalysis has a poor sensitivity and detects only 25% to 67% of UTIs demonstrated by culture, although it has an excellent specificity (97% to 100%) (227,228). Similarly, the nitrite dipstick test has a poor sensitivity (50%), despite a specificity that ranges from 97% to 100% (227,228). Thus, these tests are less than ideal for prenatal screening despite their lower costs (7,13). Of the commonly available rapid screening tests, Gram stain was demonstrated by Bachman et al. (227) to be the best, with a sensitivity of 90% and a specificity of 88%. However, as noted by Millar and Cox (93), Gram staining is relatively expensive and technician dependent (in most clinical scenarios).

As described previously (in the “Diagnosis” section), multiple new diagnostic techniques have been introduced into clinical practice with the goal of improving screening for UTI. None of these rapid screening techniques such as the Uricult dipslide paddle, Cult-Dip Plus, and Uristat test, or the bioluminescence assays meet the requirements of a good screening test (93). Recently, Hagay et al. (98) reported encouraging results combining Uriscreen (Diatech Diagnostics Ltd., Kiryat Weizmann, Ness Ziona, Israel), a rapid enzymatic urine screening test, with urine culture to confirm positive results in pregnant women. Uriscreen had a sensitivity of 100%, a specificity of 81%, a negative predictive value of 100%, and a positive predictive value of 30%. The excellent negative predictive values can avoid the use of urine culture in patients with negative screening test results with resultant substantial cost savings. However, urine culture is required to confirm positive results. Confirmation of these results in other studies is required.

Although more costly than rapid tests, culture of urine remains the screening test of choice for detecting ASB in pregnant patients. Screening for ASB with a midstream clean-catch urine culture should be obtained at the first prenatal visit (93,194,195 and 196). Among women whose cultures are negative at the initial screen, only 1% to 1.5% acquire bacteriuria later in pregnancy (148,155). Thus, repeated screening is not recommended if the initial culture is negative.

Treatment Of Asymptomatic Bacteriuria In Pregnancy

Since, at a minimum, bacteriuria predisposes the pregnant woman to acute pyelonephritis, it is a potential hazard to the fetus. Thus, detection and treatment of ASB provides the obstetrician with an ideal opportunity to prevent a significant medical complication of pregnancy. Screening at the original antenatal visit, in combination with appropriate treatment and eradication of bacteriuria, will result in prevention of 70% to 80% of all antenatal acute pyelonephritis (8,93). Such a reduction, with its attendant decline in risk to mother and fetus, is by itself sufficient justification for such a screening program. The impact of decreasing the rate of

preterm births and low-birthweight infants provides further justification (146,215).

Treatment should be designed to maintain a sterile urine throughout pregnancy, with the shortest possible course of antimicrobial agents to minimize the toxicity of these drugs on mother and fetus. Most antibacterial agents are excreted by glomerular filtration, and as a result, therapeutic concentrations are readily achieved in the urine. The concentrations of these drugs in the urine greatly exceed the concentration required for the treatment of most UTIs. Even those drugs that do not have a therapeutic concentration in the serum, such as nitrofurantoin, are present in significant concentrations in urine. Although all pregnant women should be screened and treated for bacteriuria, the treatment of choice and duration of treatment are controversial subjects (24,93).

Various antimicrobial agents are available for the treatment of ASB in pregnancy. b Lactam antibiotics such as penicillins and cephalosporins have no known fetal risks and thus can be safely used at any time during pregnancy. Other commonly used antimicrobial agents in pregnant women with ASB include short-acting sulfonamides such as sulfisoxazole and nitrofurantoin. Because sulfa competes with bilirubin for binding on albumin, sulfonamides should be used with caution during pregnancy. The fetal risk for hyperbilirubinemia and kernicterus is theoretic and occurs with sulfonamide ingestion near the time of delivery. Thus, some authors recommend that its use should be limited to the first and second trimesters. With nitrofurantoin, the fetus with glucose-6-phosphate dehydrogenase deficiency is at risk for hemolysis. Recently, a case of nitrofurantoin-induced pulmonary toxicity with respiratory failure in a pregnant patient was reported (229). However, pulmonary complications due to nitrofurantoin are very rare (0.00018%) (230). Trimethoprim-sulfamethoxazole is a frequently used agent for treating UTIs in nonpregnant women and has become common in pregnancy. The newer fluoroquinolones are not approved for use in pregnancy because of its teratogenic effect on fetal cartilage.

Early studies advised continuous therapy until delivery because of the high rate of recurrence with short courses of treatment and with such an approach documented eradication of bacteriuria in 60% to 82% of pregnant women (148,158,160,170). Subsequent investigations demonstrated that short courses of treatment (1 to 3 weeks) with sulfonamides, ampicillin, cephalosporins, or nitrofurantoin are as effective as continuous therapy in eradicating bacteriuria and eliminate the bacteriuria in 79% to 90% of patients (159,164,166,169,173,216). No single agent seems uniquely better than any other. Thus, patients with ASB should be treated with a short course of oral antimicrobial agent. Single-dose therapy is not as effective in pregnant patients as it is in nonpregnant patients, and it is not as effective as 3-day or 7-day courses (231,232 and 233). Various antimicrobial agents and treatment regimens have been used in the treatment of ASB in pregnancy. The initial selection of an antimicrobial agent is empiric. *E. coli* remains overwhelmingly the most common pathogen in ASB in pregnancy (8,93). Unfortunately, 25% to 70% of *E. coli* isolates demonstrate *in vitro* resistance to ampicillin and sulfonamides (7). The drugs that have proven to be safe and effective in the treatment of ASB of pregnancy are listed in Table 15.24.

Urinary Tract Infection	Antimicrobial Agent	Dosage
Asymptomatic bacteriuria or acute cystitis	Trimethoprim-sulfamethoxazole	160/800 mg q12h for 3 d
	Nitrofurantoin	100 mg q6h for 3 d
	Cefixime	400 mg q24h for 3 d
	Cefpodoxime proxetil	100 mg q12h for 3 d
Suppressive therapy	Nitrofurantoin	100 mg before sleep, at bedtime
	Trimethoprim-sulfamethoxazole	160/800 mg before sleep, at bedtime

TABLE 15.24. ANTIMICROBIAL TREATMENT OF URINARY TRACT INFECTIONS DURING PREGNANCY

When the presence of ASB is detected, treatment should be instituted with a 3-day course of trimethoprim-sulfamethoxazole, nitrofurantoin, cefixime, or cefpodoxime proxetil (Fig. 15.6). In geographic areas where *E. coli* remains susceptible, alternative agents include amoxicillin (250 to 500 mg q8h for 3 days), sulfisoxazole (2 g initial dose followed by 1 g q6h for 3 days), or cephalexin (250 to 500 mg q6h for 3 days). When short courses of therapy are prescribed for ASB during pregnancy, continuous surveillance of the patients for recurrent bacteriuria by repeated urine cultures is essential. If infection recurs, the patient should be maintained on suppressive antimicrobials for the remainder of the pregnancy. A single daily dose of nitrofurantoin (100 mg), preferably after the evening meal, is recommended. Alternatively, a single tablet of trimethoprim-sulfamethoxazole may be prescribed. In geographic regions with susceptible *E. coli,* amoxicillin (250 mg at bedtime) or sulfisoxazole (500 mg at bedtime) may be used for suppression.

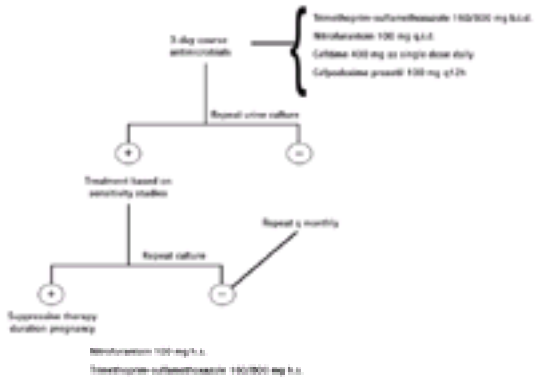


FIGURE 15.6. Management plan for asymptomatic bacteriuria in pregnancy.

The recurrence of bacteriuria during the same pregnancy has been detected in 16% to 33% of women. Our policy is that patients with recurrent ASB should be treated

with antimicrobials on the basis of the microorganism's sensitivities and then should remain on suppressive antimicrobial therapy for the remainder of the pregnancy and for 2 weeks postpartum. Others have treated recurrence with a second short period of therapy with favorable results. The effectiveness of therapy for ASB is best documented by reports demonstrating that treatment of ASB significantly decreases the incidence of acute pyelonephritis (8,93,94,214,231) and preterm birth and low birthweight (146,215).

Cystitis In Pregnancy

Acute cystitis during pregnancy is a distinct clinical entity. The diagnosis of acute cystitis is based on urinary urgency and frequency, dysuria, and suprapubic discomfort in the absence of systemic symptoms, such as fever and costovertebral angle tenderness. Gross hematuria may be present; the urine culture is invariably positive for bacterial growth. It is important to recognize that only approximately 50% of women presenting with dysuria or other lower urinary tract symptoms will have bacteriologic confirmation of a UTI (234). Those cases with symptoms of urinary infection but without bacteriologic evidence of infection are classified as having the acute urethral syndrome, which is in many instances associated with chlamydial infection. Thus, bacterial confirmation is crucial to establishing a diagnosis of acute cystitis. Traditionally, quantitative urine cultures were the gold standard and more than 100,000 colonies per milliliter is the significant count. Stamm et al. (15) established that in acutely dysuric patients, a count of <XX>100 colonies per milliliter was sufficient for diagnosing acute cystitis. Multiple dipstick culture or nitrite test techniques have been used to simplify and decrease the cost of screening urine for bacteria, and although appropriate for diagnosing acute cystitis in nonpregnant patients, in pregnancy the gold standard remains culture (93).

The reported incidence of acute cystitis in pregnancy ranges from 0.3% to 1.3% (235,236). Harris and Gilstrap (235) reported that although the increased diagnosis and treatment of ASB resulted in a decreasing incidence of pyelonephritis at their institution, the incidence of acute cystitis remained constant. On initial screening of urine cultures during prenatal care, 64% of patients who developed cystitis had negative cultures. This is in contrast to the patients with acute pyelonephritis, in which only a minority had negative initial screening cultures. These authors noted that the recurrence pattern of patients with acute cystitis differed from that of patients with either bacteriuria or acute pyelonephritis. Whereas 75% of patients with acute pyelonephritis developed a recurrence if not given suppressive antimicrobial therapy, and one third of patients with ASB subsequently developed positive urine cultures as evidence of recurrence, only 17% of patients with acute cystitis developed subsequent positive cultures (235). They reported that only 6% of patients with acute cystitis had a positive fluorescent antibody test result, suggesting upper urinary tract involvement; this is in comparison to the nearly 50% of patients with ASB and the two thirds of the patients with acute pyelonephritis who had positive fluorescent antibody test results and, presumably, renal bacteriuria. This low incidence of renal involvement may well explain the decreased likelihood for recurrence among patients with acute cystitis.

The cases of acute cystitis tended to occur in the second trimester (235). This is in contrast to reports that put most cases of acute pyelonephritis in the first and third trimester and almost all cases of ASB in the first trimester. The only morbidity associated with acute cystitis in pregnancy is the discomfort present with

symptomatic UTIs (93). No studies, to date, have demonstrated that cystitis increases the risk for preterm birth, low birthweight, or acute pyelonephritis (93). In fact, Harris and Gilstrap (235) did not have a single case of acute pyelonephritis after acute cystitis in their series.

Pregnant patients with acute cystitis should begin immediate therapy. The antimicrobial agents recommended for treatment of acute cystitis are similar to those for ASB. The recommended dosage schedules for these agents are listed in Table 15.24. The new fluoroquinolone agents are very effective agents for UTIs but are not approved for use in pregnancy.

The most commonly isolated microorganisms from the urine in patients with acute cystitis have been *E. coli* and other Gram-negative facultative organisms, such as *Klebsiella, Proteus,* or *Enterobacter*; less commonly, group B streptococcus and *S. saprophyticus.* Unlike in nonpregnant women with acute cystitis, in pregnancy, a culture should be obtained before instituting empiric therapy. Either a catheterized specimen or a clean-catch midstream urine should be obtained, before the institution of antibiotics, for urinalysis and urinary culture and sensitivities. The duration of therapy of cystitis is 3 days. Because of the symptomatology associated with acute cystitis, it is not possible to wait for the results of the culture; therefore, the constellation of symptoms and a urinalysis (or dipstick test, leukocyte esterase and nitrite) revealing white blood cells and bacteria should be sufficient to initiate therapy. The physician must obtain follow-up culture for examination of the urine to determine the effectiveness of therapy.

Acute Pyelonephritis In Pregnancy

Epidemiology

Acute pyelonephritis is one of the most frequent medical complications of pregnancy. The overall incidence is reported to be between 1% to 2.5% of all obstetric patients, with an estimated recurrence rate of 10% to 18% during the same gestation (8,93). The incidence varies depending on the population, prevalence of ASB, and whether screening for and treatment of ASB in pregnant patients occurs. Predisposing factors for acute pyelonephritis during pregnancy include obstructive and neurologic diseases of the urinary tract, ureteral or renal calculi, and previous episodes of pyelonephritis and ASB of pregnancy, which is the major predisposing factor. As screening for and treatment of ASB increases, the incidence of pyelonephritis decreases (94,213,214).

Diagnosis

Diagnosis of pyelonephritis is based on a history of shaking chills, fever, and flank pain, symptoms and signs of nausea and vomiting, frequency, urgency, and dysuria, physical findings showing costovertebral angle tenderness and fever, and laboratory reports reveling pyuria and bacteriuria. White blood cell casts on urinalysis are strong support for the diagnosis. Leukocytosis is often present. The diagnosis is confirmed by a positive urine culture. Pregnant women with pyelonephritis generally present with clear-cut signs and symptoms that allow one to easily make the diagnosis (219). Most women will have chills and documented fever and will complain of back pain (85%). A significant number (40%) of patients have symptoms of lower UTI, such as

dysuria and frequency. Almost one of four has nausea and vomiting. Fever is universal, and the diagnosis should be suspect if this is not present. Although blood cultures are positive in 10% to 15% of pregnant women with acute pyelonephritis, their usefulness in uncomplicated acute pyelonephritis has been questioned (93,237). MacMillan and Grimes (237) noted that blood cultures are expensive, the organism isolated is invariably the same as that recovered from urine, and change of antibiotics is usually based on lack of clinical response, not culture results.

Complications

Pyelonephritis poses a serious threat to maternal and fetal well-being. Maternal complications are primarily the result of bacterial endotoxin-induced tissue damage (93). Cox and Cunningham (238) noted that up to one fourth of pregnant women with severe pyelonephritis have evidence of multisystem derangement. Hemodynamic changes due to endotoxemia and hypovolemia secondary to dehydration result in hypotension. Although bacteremia occurs in approximately 10% to 15% of pregnant women with severe pyelonephritis, full-blown septic shock is rare. However, hypotension and decreased perfusion secondary to endotoxemia may not respond to fluid resuscitation alone, as well as hypotension secondary to dehydration from fever and vomiting. Such patients will present with the full-blown septic shock syndrome (238).

Moderate to severe anemia can occur as the result of hemolysis initiated by endotoxemia (239,240). Anemia has been noted in 25% to 66% of pregnant patients with pyelonephritis (206,241). Mild evidence of disseminated intravascular coagulation (thrombocytopenia and elevated fibrin split products) may be present.

Approximately 25% of pregnant women with pyelonephritis have renal dysfunction as documented by decreased creatinine clearance (242). The renal dysfunction associated with acute pyelonephritis is transient and clears over a few days (93). If the initial creatinine clearance is elevated, fluid resuscitation should be initiated and serial serum creatinine clearance tested. In addition, antibiotics with potential nephrotoxicity should be withheld or administered in reduced dosages and those excreted via the kidney administered in reduced dosages (93).

Approximately 1% to 2% of pregnant women with severe pyelonephritis develop respiratory insufficiency (238,243). The pulmonary injury is analogous to adult respiratory distress syndrome (ARDS) (shock lung) and is the result of endotoxin producing altered alveolocapillary membrane permeability, leading to pulmonary edema. Thus, pregnant women with acute pyelonephritis should be monitored closely for dyspnea and tachypnea. In most cases, these pulmonary effects are transient (238). Cunningham et al. (244) reported that evidence of pulmonary injury and respiratory insufficiency occurred in 2% of women with severe antepartum pyelonephritis. Towers et al. (245) noted an incidence of 8% if tocolysis was given to suppress uterine contractions. ARDS is life threatening, so close attention must be paid to the respiratory rate and other evidence of respiratory compromise or failure. The presence of tachypnea or dyspnea requires prompt chest x-ray and arterial blood gas analysis. Prompt recognition and appropriate intervention, including intubation and mechanical ventilation, are necessary to prevent severe hypoxemia resulting in fetal death or preterm delivery. Towers et al. (245) compared 11 patients with pyelonephritis and pulmonary injury with 119 patients with pyelonephritis only. The presence of maternal tachycardia (more than 110 beats per minute) and a fever

of 103°F 12 to 24 hours before the occurrence of respiratory symptoms in a gestation of more than 20 weeks was highly predictive of pulmonary injury (245). In this study, the most significant predictive factors associated with pulmonary injury were aspects of treatment including fluid overload, use of tocolytic agents, and choice of antibiotic (e.g., ampicillin).

As discussed already, the major fetal complications associated with acute antepartum pyelonephritis are preterm birth and low birthweight (3,13,18,21,22,162,199,200,201,202,203,204,205,206 and 207). Aggressive antimicrobial therapy and judicious tocolytic therapy may decrease this risk. However, the optimum approach is prevention of acute pyelonephritis by screening for and treating ASB in pregnant women (213,214 and 215).

Treatment

Obstetric patients with acute pyelonephritis require hospitalization for vigorous treatment with intravenous fluids and parenteral antimicrobial agents and close monitoring of renal function and respiratory status (Table 15.25). Nausea, vomiting, anorexia, and pyrexia frequently result in severe dehydration. An indwelling Foley catheter should be placed to obtain urine for microscopic examination and culture, as well as to closely monitor urine output. (Once the patient is stable and has adequate urine output, the Foley catheter can be discontinued.) Intravenous fluids are instituted promptly, and fluid replacement with isotonic crystalloid solutions should be given until adequate urine flow is established. Either Ringer's lactate or normal saline is used, and 2,000 mL often must be administered before adequate hydration is evident (i.e., improved urine output). If septicemia with shock is present, the amount of fluids required to restore isovolume may be considerably larger.

1. Hospitalization
2. Urine and blood cultures[a]
3. Complete blood count, serum creatinine, electrolytes
4. Frequent monitoring of vital signs including respiration
5. Monitor urine output (catheter if necessary)
6. Intravenous crystalloid fluid resuscitation to maintain a minimum urine output of ≥30 mL/hr
7. Intravenous antimicrobial agents
8. Chest x-ray and arterial blood gases if dyspnea or tachypnea are present

[a]Blood culture is not recommended by some investigators.

TABLE 15.25. MANAGEMENT OF PREGNANT WOMEN WITH ACUTE PYELONEPHRITIS

As noted already, approximately 25% of pregnant women with pyelonephritis have transient renal dysfunction, as documented by decreased creatinine clearance (242). This factor is particularly important when the antimicrobial agents used are

nephrotoxic, eliminated by the kidney, or both.

The initial choice of antimicrobial agent for the treatment of acute pyelonephritis is empiric (Table 15.26). This choice should be based on knowledge of the common etiologic agents and recognition of the need for bactericidal agents. The most common isolates recovered from pregnant women with pyelonephritis are *E. coli* (80% to 85%), rather than organisms of the *Klebsiella-Enterobacter* group and *Proteus* sp (8,93). Both the enterococci and the group B streptococci are increasingly recognized as pathogens in acute pyelonephritis of pregnancy. In the past, empiric therapy with ampicillin (1 to 2 g intravenously every 6 hours) or cephalothin (in similar doses) was sufficient. Because of increasing resistance of *E. coli* to ampicillin, this agent is no longer recommended as single-agent therapy of acute pyelonephritis in pregnancy. In many geographic areas, high-level resistance to first-generation cephalosporins has emerged. As an example, Millar et al. (247) noted that 12% of *E. coli* isolates from patients with pyelonephritis were resistant to cefazolin. However, Dunlow and Duff (246) reported that cefazolin was very effective for treating acute pyelonephritis. More recently, we have recommended that empiric therapy for acute pyelonephritis during pregnancy be instituted using ceftriaxone (1 to 2 g intravenously as a single daily dose). This third-generation cephalosporin provides coverage against the major uropathogens (except *Enterococcus*) and can be administered once daily, which facilitates home parenteral therapy and lowers the cost. In a prospective randomized trial, Sanchez-Ramos et al. (248) demonstrated that daily single-dose intravenous ceftriaxone was as effective as multiple-dose cefazolin in the treatment of acute pyelonephritis in pregnancy.

1. Ceftriaxone 1–2 g i.v. q24h
2. Trimethoprim-sulfamethoxazole 160/800 mg i.v. q12h
3. Ampicillin 1–2 g i.v. q6h plus gentamicin 1 mg/kg q8h
4. Cefazolin 1–2 g i.v. q8h plus gentamicin 1 mg/kg q8h[a]

i.v., intravenous.
[a]Some authors use cefazolin as a single agent.

TABLE 15.26. TREATMENT OF ACUTE PYELONEPHRITIS IN PREGNANT WOMEN

A combination of either ampicillin or cefazolin with gentamicin is an alternative choice. These combinations are appropriate for the following reasons: (a) There has been a steadily increasing pattern of resistance by *E. coli* to ampicillin and first-generation cephalosporins; (b) women with recurrent infections (or occasionally initial infections) are more likely to have microorganisms resistant to ampicillin or first-generation cephalosporins (e.g., *Enterobacter* or *Klebsiella*); and (c) the high probability for bacteremia or endotoxin sepsis argues for inclusion of a bactericidal agent that is effective against a wide range of Gram-negative facultative bacteria

including resistant organisms such as *Klebsiella, Enterobacter, Pseudomonas,* or *Serratia.* Because either group B streptococci or enterococci are responsible for a small percentage of acute pyelonephritis in pregnancy, we prefer the ampicillin-gentamicin combination, which covers these two pathogens as well. As in nonpregnant patients, trimethoprim-sulfamethoxazole (160/800 mg intravenous every 12 hours) is another effective antimicrobial regimen for treating pyelonephritis in pregnancy. Recently, Wing et al. (249) conducted a randomized prospective trial of the treatment of pyelonephritis in pregnancy comparing three antibiotic regimens: (a) intravenous ampicillin and gentamicin; (b) intravenous cefazolin; and (c) intramuscular ceftriaxone. There were no statistically significant differences in clinical response or birth outcomes among the three regimens for treating acute pyelonephritis in pregnancy before 24 weeks of gestation.

Intravenous antibiotics are continued until the patient is afebrile for 24 to 48 hours and can tolerate oral medications. With prompt treatment, a rapid clinical response occurs and most patients are afebrile and asymptomatic within 48 hours. Monitoring of serum levels of gentamicin is crucial in pregnancy, in which the associated increase in vascular volume and glomerular filtration rate results in a high prevalence of subtherapeutic serum levels with aminoglycosides (250). Peak levels of gentamicin should be less than 10 µg/mL and the trough level should be less than 2 µg/mL. We recommend obtaining peak and trough serum levels approximately 24 hours after initiation of therapy, and if these levels, together with the serum creatinine clearance, are within the reference range, one should repeat these evaluations every 3 days. After intravenous antimicrobial therapy, 85% of patients become afebrile within 48 hours, and nearly 100% of patients do so within 4 days (219). If this does not occur and the patient continues to be febrile, it must be assumed that resistant organisms are present or obstructive uropathy with or without calculi exists. A change or an addition of antimicrobial agents may be necessary, based on the sensitivities of the microorganisms recovered on urine culture.

Investigation should be undertaken to rule out obstructive lesions of the urinary tract in patients not responding within 48 to 72 hours. A “one-shot” intravenous pyelogram or real-time ultrasonography should be used. Few patients will develop a perinephric abscess, which requires surgical drainage.

Angel et al. (251) proposed that pregnant women with acute pyelonephritis could be treated solely with oral antimicrobial agents. In a randomized trial of oral cephalexin versus intravenous cephalothin, Angel et al. (251) reported equal efficacy rates (91% vs. 93%). However, 13 (14.4%) of the patients were bacteremic and thus were excluded. When the bacteremic patients were included, oral therapy was only effective in 32 (71%) of 45 patients, compared with 39 (87%) of 45 patients in the intravenous group. Subsequently, Millar et al. (247) performed a randomized controlled trial comparing inpatient and outpatient treatment of pregnant women with acute pyelonephritis before 24 weeks of gestation. The patients were initially observed in the emergency department to verify that they were stable and able to tolerate oral intake. The patient group (n = 60) received intravenous cefazolin and the outpatients (n = 60) received ceftriaxone (1 g intramuscularly in the effective dose and 1 g intramuscularly at home within 18 to 36 hours after discharge), followed by oral cephalexin (500 mg four times a day to complete a 10-day course). Home health care nurses monitored the patients' progress for 48 to 72 hours after initial treatment. Patients with evidence of severe pyelonephritis were excluded from the study. Rates of persistent or recurrent bacteriuria and recurrent pyelonephritis were

the same in both groups (247). Six (10%) of the inpatients were switched to gentamicin because of failure to respond to cefazolin, whereas none of the outpatients required a change in antibiotic ($p < 0.03$). Although on the surface, this study suggests that outpatient antibiotic therapy may be an appropriate option for selected pregnant women with pyelonephritis, the inpatient arm was inferior, as 12% of *E. coli* isolates were resistant to cefazolin (247), thus biasing the results in favor of the ambulatory regimen. Moreover, this study incorporated close monitoring, stabilization for up to 24 hours in the effective dose, and home visits. Thus, extrapolation to general clinical practice is difficult.

More recently, Wing et al. (46) compared outpatient management with inpatient management of pyelonephritis in pregnancy beyond 24 weeks of gestation (46). All patients received two 1-g doses of ceftriaxone intramuscularly at 24-hour intervals while hospitalized. The outpatients were discharged after 24 hours of hospital observation if they were stable and prescribed cephalexin (500 mg orally four times a day for 10 days). Inpatients received oral cephalexin until they were afebrile for 48 hours and then were discharged to complete a 10-day course of oral cephalexin. There were no significant differences in clinical responses or birth outcomes of inpatients or outpatients if they completed their assigned protocol (46). However, 30% of outpatients were unable to complete their protocol. Moreover, most women with acute pyelonephritis were not candidates for outpatient therapy because of suspected sepsis (blood pressure of less than 90/50 mm Hg, temperature of more than 39.8°C, or sustained tachycardia of 110 beats per minute), signs of ARDS, serious underlying medical disorders (such as diabetes and systemic lupus), renal or urologic disorders, or intolerance of oral intake.

Because of concerns with the previously discussed studies, our policy is that pregnant women with pyelonephritis at any gestational age should be hospitalized for initiation of antimicrobial therapy, rehydration, close monitoring for complications, and monitoring for preterm labor. Once patients have stabilized and are afebrile for 24 to 48 hours, they are discharged on oral therapy to complete a 10-day course.

Recurrence for acute pyelonephritis during the same gestation has been reported in 10% to 18% of all patients with pyelonephritis. In a retrospective analysis, Harris and Gilstrap (252) reported that patients with acute pyelonephritis who did not receive suppressive antimicrobial therapy for the remainder of the gestation had a 60% incidence of recurrence, requiring rehospitalization. This was in contrast to the low incidence (2.7%) of recurrence and rehospitalization in patients who were maintained on suppressive antimicrobial therapy for the duration of the gestation. Cunningham et al. (198) noted a similar high incidence of recurrence among patients not receiving suppressive therapy. Lenke et al. (253) performed a prospective randomized trial assessing antibiotic prophylaxis after an episode of pyelonephritis during pregnancy versus use of sequential urine cultures to identify patients for re-treatment. These authors noted that recurrent or persistent bacteriuria was more common in the group followed with sequential cultures. However, the rates of recurrent pyelonephritis in the two groups were similar, 7% and 8%. Suppression is accomplished with nitrofurantoin, 100 mg each, or trimethoprim-sulfamethoxazole, 80/160 mg every night before bed (Table 15.24). An acceptable alternative to suppressive therapy is continued examination every 2 weeks of urine cultures for the detection and prompt treatment of recurrent bacteriuria. We feel that the risk of recurrence of pyelonephritis is too great not to suppress the UTI with antimicrobial therapy after an

acute episode of pyelonephritis.

Nosocomial Urinary Tract Infection

Epidemiology

Hospital-acquired UTIs are among the most frequent of nosocomial infections. An exact prevalence for nosocomial UTIs is difficult to come by because of various surveillance systems and different definitions (i.e., clinically manifest infection versus laboratory evidence of significant bacteriuria). Based on data obtained from surveillance studies of nosocomial infections, approximately one third of these hospital-acquired infections involve the urinary tract (254,255,256,257 and 258). Sixty percent of the nosocomial infections occurring in gynecologic patients involve the urinary tract (259). Current estimates are that approximately 500,000 patients per year acquire UTIs in acute care hospitals in the United States (260,261). Most of these UTIs are associated with usage of indwelling urethral catheterization or other types of urinary instrumentation (262,263).

It has been estimated that 1% of nosocomial UTIs (i.e., 5,000 cases) are associated with bacteremia and potentially life-threatening illness (265). Platt et al. (266) report that the acquisition of UTI during indwelling bladder catheterization is associated with nearly a threefold increase in mortality rate among hospitalized patients. These investigators concluded that 14% of the deaths among the catheterized patients represented the excess mortality that was associated with acquisition of infection. Based on estimates that nearly 400,000 deaths per year occur in the approximately 7.5 million persons catheterized annually in the United States, they estimated that the excess mortality associated with catheter-related infection is 56,000 patients per year.

Etiology And Pathogenesis

As in other UTIs, *E. coli* is the most common etiologic agent in nosocomial infections involving the urinary tract; it accounts for approximately 50% of nosocomial bacteriuria cases (267). The *Klebsiella-Enterobacter* group of organisms are recovered in 13% to 15%, *Proteus* sp in 3% to 13%, and *Pseudomonas aeruginosa, Serratia,* enterococci, staphylococci, and yeast make up the remainder of etiologic agents (265,267,268,269 and 270). *E. coli* and the *Klebsiella-Enterobacter* group tend to occur among patients who have not received antimicrobial therapy. Among patients who are debilitated, immunosuppressed, or on antibiotic therapy, organisms such as *Proteus, Pseudomonas, Serratia, Enterococcus,* and yeasts are recovered with greater frequency. Stamm et al. (258) reported that *Serratia* and *Klebsiella* are associated with an inordinate frequency of bacteremia.

It has been estimated that 75% to 80% of nosocomial bacteriuria cases follow urinary tract catheterization (258,263,264). Certain risk factors have been identified, which are unavoidable; these include increasing age, debilitating illness, and female sex. Turck and Stamm (265) also described additional factors involved in the risk of acquiring bacteriuria, which are alterable. These factors relate to both the method and the duration of catheterization. Thus, a single in-and-out catheterization is associated with an incidence for infection of less than 1%, whereas 100% of patients with indwelling urethral catheters draining into an open system for more than 4 days

develop bacteriuria (1,270). Garibaldi et al. (267) noted that even with use of a closed drainage system, the risk of infection increased 5% to 10% per day of catheterization.

Bacteria that cause catheter-associated UTI gain access to the urinary tract by three major routes. The first is introduction of microorganisms from the external genitalia or distal urethra into the bladder at the time of catheterization. In general, bacteria introduced in this way are well tolerated and controlled by voiding and the antibacterial defense mechanism of the bladder (265). A second mechanism by which bacteria gain access to the bladder is via a thin film of urethral fluid on the outside of the catheter (271). Catheters have been shown to contain biofilm on their surface (272,273). Bacteria contained within such biofilms are protected from antibiotics and the natural defense provided by flow of urine (274). Third, once the drainage system has been contaminated, bacteria may migrate up inside the catheter lumen (267,268). Turck and Stamm (265) believe that the intraluminal ascending route accounted for most nosocomial UTIs. Such contamination may be due to failure to use sterile technique in disconnecting the catheter and drainage tube to obtain a specimen or to irrigate the catheter (259). Inadvertent disconnection occurs and frequently results in contamination. An additional important factor in the pathogenesis of catheter-associated UTI is cross-contamination of catheters by transmission of bacteria from patient to patient on the hands of hospital personnel (1,259).

Treatment And Prevention

In general, we do not use antimicrobial agents to treat those patients in whom bacteriuria occurs during catheterization, but who remain asymptomatic. This concern relates to the risk of persistent colonization or emergence of more resistant nosocomial organisms. Fortunately, in many such situations, removal of the catheter results in eradication of the bacteriuria. If signs and symptoms of cystitis or acute pyelonephritis occur with the presence of an indwelling catheter, systemic antimicrobial therapy should be administered for 10 to 14 days. In addition, if bacteriuria without symptoms persists once the catheter is removed, treatment should be initiated. Regimens similar to those used in treating acute cystitis are appropriate for this situation (Table 15.24).

The most important and effective method for prevention of nosocomial UTIs is to limit the use of indwelling catheters only to instances in which they are necessary. Additional preventive measures have been recommended (259): (a) Urinary catheters should be removed as soon as possible; (b) only adequately trained hospital personnel should insert urinary catheters; (c) use of aseptic technique in inserting catheters to avoid introducing bacteria; (d) cleansing the metal catheter junction with soap and water once or twice a day to reduce periurethral bacterial contamination; (e) maintain unobstructed “downhill” flow in a closed drainage system; (f) disconnect the drainage system only to irrigate an obstructed catheter, not to obtain specimens or to routinely irrigate; and (g) whenever feasible, separate catheterized patients from each other to prevent cross-contamination.

Proposed measures to aid in prevention but for which supporting data are lacking to demonstrate an advantage over a closed drainage system include the following: (a) a flutter valve to prevent reflux of urine from the collection bag to the drainage tube; (b) continuous bladder irrigation via a triple-lumen catheter with either acetic acid or a

neomycin-polymyxin solution; (c) use of suprapubic catheterization; and (d) prophylactic systemic antibiotics.

The final aspect of catheter care is to obtain a follow-up culture after the catheter is removed and to institute appropriate antimicrobial therapy if significant bacteriuria persists after removal of the catheter.

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16

PERINATAL INFECTIONS

VIRUSES

Rubella

Rubella (also known as German measles) is usually a mild viral illness with fever, postauricular or suboccipital lymphadenopathy, arthralgia, and a transient erythematous rash. It has been gratifying that since 1966, the incidence rate of reported rubella cases has fallen dramatically from 28 cases per 100,000 population to approximately 1 case per 100,000 in 1982 (1). Yet, there was a resurgence of rubella and congenital rubella syndrome (CRS) from 1989 to 1991, with outbreaks continuing to occur. By 1992 and 1993, however, the reported number of cases of rubella was the lowest ever (2). Further, in 1996, there were only 238 cases of rubella reported in the United States and only 4 cases of CRS (3). Since Gregg, an Australian ophthalmologist, observed in 1941 that rubella in early pregnancy was teratogenic, this disease has been of special concern to the obstetrician.

Epidemiology

Wild rubella virus is spread by droplets or direct contact with infected persons or articles contaminated with nasopharyngeal secretions. Although it is considered primarily a disease of childhood, in the past few years, more than half the cases have occurred in patients older than 9 years. From 1992 through 1997, 65% of reported cases of rubella occurred in individuals 20 years or older (5). With so large

a percentage in adults of reproductive age, those providing care must have a heightened awareness about rubella (2). By reproductive age, about 75% to 85% of the population has had rubella, and about half of the cases are subclinical infections. Once wild virus infection occurs (even if subclinical), immunity is lifelong.

Before vaccination became available in 1969, rubella occurred in 6- to 9-year cycles, but the last major epidemic was in 1964. Since 1982, the rate in the United States has been less than 1 case per 100,000 population; but outbreaks occur, particularly among members of religious communities that traditionally refuse vaccination (Fig. 16.1). In 1991, these groups in Michigan, New York, Ohio, Pennsylvania, and Tennessee accounted for approximately 90% of the 1,007 cases in the United States. Since 1992, outbreaks have occurred among young adults in specific racial/ethnic groups (for example, Hispanics and Asian/Pacific Islanders) who frequently have not been vaccinated and in persons who have immigrated from countries, such as Brazil and Mexico, where vaccination is not routine.

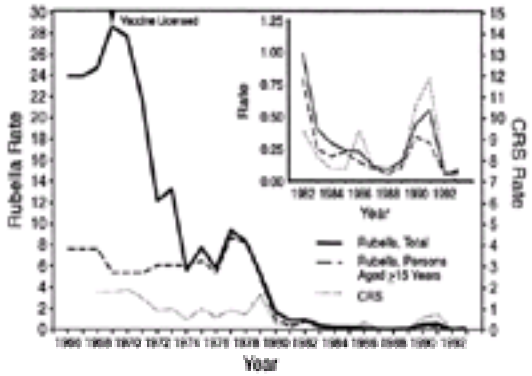


FIGURE 16.1. Incidence rates of rubella and congenital rubella syndrome (CRS) in the United States, 1966 to 1993. Cases of rubella were reported to the National Notifiable Disease Surveillance System per 100,000 population. Cases of CRS were reported to the National CRS Registry per 100,000 livebirths. (From Centers for Disease Control and Prevention. Rubella and congenital rubella syndrome—United States, January 1, 1991–May 7, 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:397, with permission.)

The main problem is infection during early pregnancy, when primary maternal rubella may lead to involvement of the embryo or fetus. As shown in Table 16.1, the risk of CRS after maternal infection in the first trimester is as high as 85% when infants have been followed for up to 40 years. The risk of any defect decreases to approximately 50% if infection occurs during the 9th through 12th week of gestation, and the risk of CRS is low when infection occurs after the 20th week of gestation (5). In 1996, the Centers for Disease Control and Prevention (CDC) (3) revised the case definitions for rubella and CRS (Box 16.1 and Box 16.2).

Gestational Age (Wk)	Estimated Risk (%)
≤8	85
9–12	52
>20	Rare

Source: From Centers for Disease Control and Prevention. Measles, mumps, and rubella–vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1998;47:1–57, with permission.

TABLE 16.1. RISK OF CONGENITAL RUBELLA AFTER MATERNAL INFECTION BY GESTATIONAL AGE AT INFECTION

Cataracts, patent ductus arteriosus, and deafness are the most common abnormalities. When these children have been followed for a few years, additional disorders such as diabetes have occurred more frequently than expected. CRS has not been eliminated from the United States, but progress is being made. In 1969, when the vaccine was licensed, there were 62 cases of CRS in the United States. The number of cases decreased generally over the next two decades, so by the late 1980s, only one to three cases were reported per year. Then paralleling the rise in rubella overall, there was a dramatic surge in CRS cases between 1990 and 1991 to 25 and 31 cases, respectively. In 1991, two thirds of the cases occurred in infants born to Amish mothers in Pennsylvania. By 1992, there were only five cases in the United States, and in 1993—for the first time ever—there were no cases of CRS among infants born in the United States. (Not included in these reported cases are several imported cases, for example, five in 1992 and one in 1993.)

Diagnosis

With rubella infection, the virus can be isolated from the bloodstream and throat 7 to 10 days after exposure. Shedding of virus from the throat continues for about a week. The rash, which typically starts in the face, commonly develops 16 to 18 days after exposure. The diagnosis of rubella should never be based solely on clinical criteria. To confirm rubella infection, various antibody tests are available. Hemagglutination inhibition (HI) antibody, an IgG class antibody, has been most commonly used for screening, but a number of newer antibody tests have replaced the HI because of lower cost and/or greater sensitivity. The most commonly used tests are enzyme immunoassay (EIA) tests, but others include latex agglutination, fluorescence immunoassay, passive hemagglutination, hemolysis in gel, and virus neutralization (6). A number of kits have been approved by the Food and Drug Administration (FDA), but in comparative testing, not all kits are equivalent. The most important aspect of a diagnostic kit for rubella screening tests is a high specificity (i.e., a low false-positive rate), as false-positive test results could result in failure to identify susceptible women. Further, many clinical laboratories now report rubella status as simply present or not present (corresponding to immune or nonimmune). Any antibody level is considered evidence of immunity (5). Thus, when acute rubella is suspected, the laboratory must be consulted and paired serum obtained so that

quantitative antibody levels can be measured.

Also an IgG antibody, complement-fixing (CF) antibody appears later than HI antibody and may be useful in some diagnostic situations, such as in patients with high HI levels or patients first seen 1 to 5 weeks after exposure. It may thus be possible to demonstrate a significant rise in CF antibody when it is too late to demonstrate this change in HI antibody. The CF test has to be requested, because it is not performed routinely. Rubella-specific IgM antibodies appear early and last for only a few weeks. This test may be helpful in some diagnostic situations but is available in few laboratories. Although a positive rubella IgM titer indicates recent primary rubella infection, its absence does not necessarily exclude it, as in some patients, IgM may disappear in less than 4 to 5 weeks. When a patient is first seen with an elevated titer, it is not always possible to determine whether there has been acute primary rubella infection, even though these other tests are properly used (7). According to the CDC (5), persons generally can be presumed to be immune to rubella if they have documented vaccination with at least one dose of measles, mumps, and rubella (MMR) vaccine or other live rubella–containing vaccines, when administered on or after the first birthday, or if they have laboratory evidence of rubella immunity, or if they were born before 1957 (except women who could become pregnant). Birth before 1957 is not acceptable evidence for rubella immunity for women who could become pregnant because it provides only presumptive evidence of rubella immunity and does not guarantee that a person is immune. If a person has an “equivocal” serologic test result, that individual should be considered susceptible to rubella unless they have evidence of adequate vaccination or a subsequent serologic test result indicating rubella immunity. Postinfection immunity to rubella appears to be long lasting and is probably lifelong.

Box 16.1

Case definition for rubella (revised, 9/96)

Clinical case definition:

An illness that has all of the following characteristics:

- Acute onset of generalized maculopapular rash
- Temperature of more than 99.0°F (more than 37.2°C), if measured
- Arthralgia/arthritis, lymphadenopathy, or conjunctivitis

Laboratory criteria for diagnosis include the following:

- Isolation of rubella virus, or
- Significant rise between acute and convalescent phase titers in serum rubella immunoglobulin G (IgG) antibody level by any standard serologic assay, or
- Positive serologic test result for rubella immunoglobulin M (IgM) antibody

Case classification:

- Suspected: any generalized rash illness of acute onset
- Probable: a case that meets the clinical case definition, has no or noncontributory serologic or virologic testing, and is not epidemiologically linked to a laboratory-confirmed case
- Confirmed: a case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case

Comments

Serum rubella IgM test results that are false-positive have been reported in persons with other viral infections (e.g., acute infection with Epstein-Barr virus [infectious mononucleosis], recent cytomegalovirus [CMV] infection, and parvovirus infection) or in the presence of rheumatoid factor. Patients who have laboratory evidence of recent measles infection are excluded.

Box 16.2

Case definition for Congenital Rubella Syndrome (CRS) (revised, 9/96)

Clinical description:

An illness usually manifesting in infancy resulting from rubella infection *in utero* and characterized by signs or symptoms from the following categories:

- Cataracts or congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), loss of hearing, pigmentary retinopathy
- Purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease

Clinical case definition:

Presence of any defects or laboratory data consistent with congenital rubella infection

Laboratory criteria for diagnosis include the following:

- Isolation of rubella virus, or
- Demonstration of rubella-specific IgM antibody, or
- Infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer or maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month)

Case classification:

- Suspected: a case with some compatible clinical findings but not meeting the criteria for a probable case
- Probable: a case that is not laboratory confirmed and that has any two complications listed in the first clinical description paragraph or one complication from each paragraph and lacks evidence of any other etiology
- Confirmed: a clinically compatible case that is laboratory confirmed
- Infection only: a case that demonstrates laboratory evidence of infection, but without any clinical symptoms or signs

Comment

In probable cases, either or both of the eye-related findings (i.e., cataracts and congenital glaucoma) are interpreted as a single complication. In cases classified as infection only, if any compatible signs or symptoms (e.g., hearing loss) are identified later, the case is reclassified as confirmed.

Counseling And Management

Pregnant women with confirmed rubella infection must have proper counseling about the risks and types of congenital anomalies. Culturing amniotic fluid for rubella virus is not advised, because this does not reliably distinguish the infected fetus from the uninfected one among pregnancies at risk.

However, the Advisory Committee to the CDC notes that immunoglobulin (Ig) given after exposure prevents neither infection nor viremia, although it may alter symptoms (5). Further, infants with congenital rubella have been born to women who received Ig shortly after exposure. Thus, the committee does not recommend Ig for routine use for postexposure prophylaxis. Yet, it suggests that Ig might be useful in susceptible, exposed pregnant women for whom pregnancy termination would not be acceptable. In this case, Ig might offer some protection against fetal infection (5).

Prevention

When the rubella virus vaccine became available in 1969, the strategy in the United States was to control rubella in preschool and young school-aged children who were known reservoirs. It was believed that this approach would prevent exposure of susceptible pregnant women to the wild virus. By 1977, however, 10% to 20% of women of childbearing age still were susceptible—a proportion similar to that in the prevaccine years. To meet the national goal of eliminating CRS by 1996, improved control strategies were necessary, particularly targeting young adults. These measures included increasing vaccination in children, implementing laws requiring vaccination among students, encouraging all providers to vaccinate young adults and adolescents, encouraging vaccination among religious groups that do not seek traditional health care, and targeting young adults who are likely to be unvaccinated (2).

In January 1979, the rubella virus vaccine RA27/3 replaced the HPV77 vaccine in the United States. All rubella virus vaccines contain live attenuated virus. RA27/3 is administered subcutaneously. After vaccination, approximately 95% of susceptible individuals develop HI antibodies, which provide long-term (probably lifelong) protection. Among adults who did not show a positive HI titer after vaccination, nearly all show detectable antibody when a more sensitive test is used. According to the CDC, any detectable rubella antibody or a history of rubella vaccination is presumptive evidence of immunity.

Those vaccinated may shed the attenuated virus from the nasopharynx for a few weeks, but there is no evidence that the vaccine virus can be transmitted. Thus, there appears to be no risk to susceptible pregnant women who contact recently vaccinated children or adults.

Rubella-susceptible women of reproductive age should be considered candidates for immunization, but it is recommended that pregnancy be avoided for 90 days. The immediate postpartum period is often suggested as an excellent time for immunization. Vaccinated women may breast-feed without fear of adverse effects to the newborn, and Rh-negative women may receive Rh_0(D) immune globulin, if

indicated, as well as the rubella virus vaccine.

It has been suggested that to eradicate CRS, one must make an increased effort to ensure that patients are either immune to rubella or vaccinated as part of routine medical and gynecologic care. For reproductive-age women, recommendations have included determining rubella immunity or vaccinating women in family planning clinics, during any hospitalization, at the time of premarital serology testing, or at college entry examinations. Rubella outbreaks in hospitals have led to the recommendation to screen for rubella immunity and vaccinate susceptible hospital employees who may have contact with pregnant women (8).

Again, it is recommended that the rubella virus vaccine not be given to pregnant women and that pregnancy be avoided for 90 days. Nevertheless, many rubella-susceptible pregnant women have received the RA27/3 rubella virus vaccine within 3 months after the time of conception. As of late 1986, 172 of these women delivered at term. After vaccination with the HPV77 preparation, the virus has been isolated from the products of conception in about 20% of the cases. With the RA27/3 vaccine, cases are fewer, but this virus appears to be isolated less frequently (approximately 3%). Even though the virus may be isolated in the products of conception, none of these cases of maternal RA27/3 vaccination resulted in any anomalies consistent with CRS. The risk of teratogenicity from the RA27/3 vaccine virus is considerably lower than that with the wild virus and has been estimated by the CDC to be 1.2% (5). The risk estimate was derived by the binomial distribution.

Side effects of the vaccine include arthralgias, but true arthritis occurred in less than 1%. In susceptible adult women, joint symptoms are more frequent and tend to be more severe than in children, but adults have not usually had to disrupt work. Other complaints such as pain or paresthesias have been rare.

Besides pregnancy, contraindications to vaccination are febrile illnesses and immunosuppression. Precautions are necessary in few individuals with neomycin allergy. Breast-feeding is not a contraindication to vaccination. Even though vaccine virus can be transmitted via breast milk to the infant, the infant remains asymptomatic (5). The eradication of CRS and rubella is feasible worldwide because of the high efficacy of the RA27/3 rubella vaccine and the low cost of vaccine outside of the United States, making it affordable except in the poorest countries. However, universal vaccination of infants without associated vaccination of adults is not likely to be successful. Efforts need to be made to strengthen postpartum vaccination of susceptible women and women at all encounters in the health care system (9).

Prenatal Diagnosis Of Congenital Rubella

To diagnose fetal infection after primary rubella infection in early pregnancy, Daffos et al. (10) obtained fetal blood under ultrasound guidance at 20 to 26 weeks of gestation in 18 patients. Rubella-specific IgM was present in 12. Of these 12 pregnancies, terminations were performed in 6 of 6 pregnancies with rubella before 12 weeks of gestation and in 2 of 6 with rubella after 12 weeks, by parental decision. Among the six fetuses with blood-negative rubella-specific IgM, one was infected at birth. The missed diagnosis was believed to be due to sampling too early in gestation (10).

Cytomegalovirus

CMV, a DNA virus of the herpesvirus group, causes cytomegalic inclusion disease. Characteristic large cells with prominent intranuclear inclusion bodies have been identified with this disease since the early 20th century, but the virus was not isolated until 1956 (Fig. 16.2). Although this “owl's eye” appearance is pathognomonic for CMV infection, these cells are relatively rare in infected individuals. Initially, CMV was considered to be rare because only the classic clinically severe form of the disease was appreciated. Subsequent studies using viral cultures have identified the frequent presence of “silent” CMV in which no clinical manifestations are present. Weller (1) initially described the scope and impact of congenital CMV. It has been estimated that there are approximately 40,000 infants born annually in the United States with congenital infection (2,3 and 4). CMV is now recognized as the most common cause of intrauterine infection, and congenital CMV infection has been reported to occur in 0.5% to 2.5% of all births in the United States (Table 16.2). An additional 3% to 5% of newborns acquire CMV during the perinatal period.

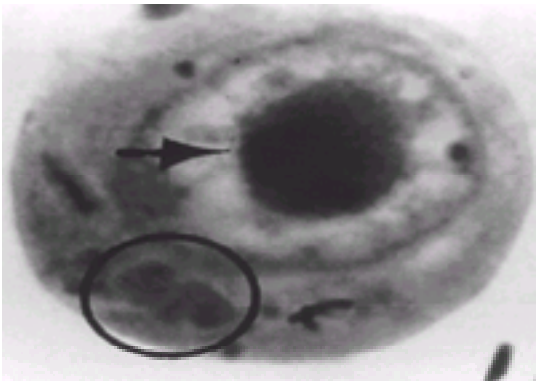


FIGURE 16.2. Intranuclear (*arrow*) and cytoplasmic inclusion (*circle*) in a pathognomonic “owl's eye” cell of cytomegalic inclusion disease.

Location	No. of Infants Screened	No. of Congenital Infections	% Congenital Infections
Manchester, England (1978)	6,051	14	0.24
Aarhus-Viborg, Denmark (1979)	3,060	11	0.36
Hamilton, Canada (1980)	15,212	64	0.42
Birmingham, Alabama (upper SES) (1981)	2,698	16	0.60
Houston, Texas (upper SES) (1980)	461	3	0.60
Rochester, New York (1976)	8,644	53	0.61*
Houston, Texas (low SES) (1981)	499	6	1.2
Abidjan, Ivory Coast (1978)	2,031	28	1.38
Birmingham, Alabama (low SES) (1980)	1,412	31	2.2

*Cord blood immunoglobulin M. SES, socioeconomic status.

TABLE 16.2. RISK OF CONGENITAL CYTOMEGALOVIRUS INFECTION

Absence of detectable infection at birth may not be innocuous. The persistent and progressive nature of these inapparent congenital infections may result in central nervous system (CNS) pathology and neurologic sequelae, which represent the major impact of CMV infection (5).

The teratogenic potential of CMV is unsettled. Although the virus can cause a reduction in the absolute number of cells in various organs, whether this is due to a direct effect on the cells or whether it is secondary to endothelial and vascular damage is not known. Malformations such as cataracts or congenital heart lesions are seldom seen with CMV. Thus, congenital CMV bears a closer resemblance to congenital toxoplasmosis, in which defects are secondary to destruction of tissue than to congenital rubella.

Epidemiology

Approximately 40% of women in the United States and Europe are susceptible to CMV by the time they reach reproductive age, and the highest rate of seroconversion occurs between the ages of 15 and 35. Socioeconomic status is a major determinant of susceptibility; only 15% of lower income women are susceptible, compared with 45% of higher income women (3). The rate of seroconversion in women in the reproductive age range is approximately 2% annually in higher socioeconomic groups, compared with 6% among lower socioeconomic groups (6). Chandler et al. (7) demonstrated that seropositivity to CMV correlated with lower socioeconomic status, multigravidity, older age, first pregnancy when younger than 15 years, and a greater number of sex partners. Absence of these risk factors identifies those women who are most susceptible to primary CMV infection during pregnancy.

In a study from Alabama, Hunter et al. (8) found that 30% to 40% of pregnant women were susceptible to CMV. Primary CMV infection, as evidenced by seroconversion, occurred in 1.6% of 8,000 pregnancies (8). CMV infection is more likely in lower socioeconomic groups. In a longitudinal study of CMV in 4,578 pregnant women in Houston, Yow et al. (9) reported that 52% had CMV antibody, and that among the susceptible women, 2.2% developed primary CMV during pregnancy. Although CMV infection is widespread, it produces serious illness only in fetuses, immunodeficient individuals, and patients receiving immunosuppressive therapy. Most adult infections are subclinical, and the remainder (approximately 10%) cause a mononucleosis-like illness.

CMV is a ubiquitous organism that has developed a remarkably successful form of parasitizing humans. It is persistently excreted and is communicable for long periods. Infants infected congenitally excrete CMV on an average of 4 years. Those acquiring CMV at the time of birth excrete the virus for 2 years. Many seropositive young adults shed CMV intermittently. Recurrent excretion of CMV in asymptomatic persons may be due to several possible mechanisms. After primary infection, a low-grade chronic infection might be established in which viral excretion periodically reaches detectable levels. Reinfection could occur in immune persons because of antigenic and genetic disparity among CMV strains. Also, like herpes simplex virus (HSV), CMV may become latent during the primary infection and in later life be reactivated by various stimuli or with suppression of the cell-mediated immune system (e.g., human immunodeficiency virus [HIV] infection, transplant recipients on

immunosuppressive medication, and pregnancy).

Asymptomatic CMV infection and excretion is common during pregnancy. The cervix is involved in 3% to 18% of cases, urinary tract in 3% to 9%, breast milk in up to 27%, and the pharynx in 1% to 2%. Overall, CMV can be cultured (cervix and urine) in 2% to 28% of pregnant women. The incidence of CMV infection is highest in low-income, young, primiparous, lower educational status, and unmarried women. Longitudinal studies have demonstrated that the average incidence of cervical excretion of CMV in pregnancy increases from 2.6% (range, 0 to 7.1) in the first trimester to 7.6% (range, 2% to 28%) near term. These asymptomatic infections occur mainly in seropositive women whose antibody status does not change in spite of viral shedding. Pregnancy itself may either increase a woman's susceptibility to CMV infection or reactivate latent infection.

Congenital CMV infection is acquired *in utero,* usually as the result of transplacental transmission of CMV. However, ascending infection from the cervix may also occur. Neonates with congenital CMV are culture positive for the virus at birth. Most commonly, CMV is excreted in urine. On average, 1% (range, 0.5% to 2.5%) of all newborns excrete CMV at birth and are congenitally infected. In addition to those fetuses, an additional 3% to 5% of liveborn infants acquire CMV peripartum, presumably as a result of exposure to infected cervical secretions, ingestion of infected milk, or exposure to infected transfused blood. If a maternal genital CMV infection is present at the time of birth, 30% to 50% of the neonates will acquire the virus. Perinatal CMV is the term applied to infants whose initial urine culture at birth is negative but have subsequent positive cultures several days to months after delivery.

The infections transmitted *in utero* are the major concern, particularly because they relate to infant development. Perinatally acquired CMV infection does not result in serious complications or sequelae except in very-low-birthweight neonates (less than 1,200 g). Congenital infections may occur after either primary or recurrent maternal infection. A demonstrably high rate of congenital infection in infants born to previously immune mothers suggests that recurrent maternal CMV is an important cause of intrauterine transmission of CMV. Indeed, as pointed out by Stagno and Whitley (3), in lower income women (approximately 85% of these women are immune), most intrauterine infections occur in immune, rather than in susceptible, women (3). In fact, the birth of an infant with congenital CMV infection does not ensure that a subsequent fetus will not become infected *in utero.* Congenital CMV has been reported in consecutive pregnancies up to 3 years apart. In a prospective study of seroimmune women, Stagno et al. (10) found that the rate of congenital CMV infection was 1.9% among 541 infants born to seropositive women (Table 16.3). Similarly, Schopfer et al. (11) reported a 1.4% prevalence of congenital CMV in a population from the Ivory Coast that was virtually 100% seropositive because of previous CMV infection.

Parameter	Total	No. Infected (%)
Incidence in general infant population	1,412	31 (2.2)
Incidence with recurrent maternal infection		
Previously seropositive	457	8 (1.8)
Prior CMV excretion	58	1 (1.7)
Prior intrauterine transmission	26	1 (3.8)
Total recurrent	541	10 (1.9)

CMV, cytomegalovirus.
Source: From Stagno S. Maternal cytomegalovirus infection and perinatal transmission. *Clin Obstet Gynecol* 1982;25:563–576, with permission.

TABLE 16.3. INCIDENCE OF CONGENITAL CMV INFECTION IN A LOW-INCOME POPULATION

However, primary CMV infection acquired during pregnancy poses a significantly more severe risk to the infant than does recurrent infection (6,13). Stagno et al. (6) reported that symptomatic congenital CMV infection occurred only with primary maternal infection and that sequelae or complications were significantly more frequent in the primary group (35% vs. 7%) (Table 16.4). In a more recent update from the Alabama group, Fowler et al. (13) again demonstrated that only infants born to mothers with primary CMV infection had symptomatic CMV infection at birth (18% vs. 0%). Sequelae were noted in 25% of the primary group, compared with 8% in the recurrent CMV infection group (13). Mental impairment (Ig level of less than 70) was noted in 13% of infants exposed to primary CMV, versus 0% in the recurrent group (13). Sensorineural hearing loss was present in 15% of infants born to mothers with primary CMV infection during pregnancy, compared with 5% of infants born to mothers with recurrent infection. Most importantly, only children born to mothers with primary CMV infection developed bilateral hearing loss (8%).

Sequelae	Type of Maternal Infection		
	Primary (%)	Recurrent (%)	P Value
Sensorineural hearing loss	18/120 (15%)	3/56 (5.4%)	.05
Bilateral hearing loss	10/120 (8.3%)	0/56 (0)	.02
IQ <70	9/68 (13.2%)	0/32 (0)	.03
Chorioretinitis	7/112 (6.3%)	1/54 (1.9%)	.20
Microcephaly	6/125 (4.8%)	1/64 (1.64%)	.26
Seizures	6/125 (4.8%)	0/64 (0)	.08
Death	3/125 (2.4%)	0/64 (0)	.29
Any sequelae	31/125 (24.8%)	5/64 (7.8%)	.003

[a]Based on Fowler KB, Stagno S, Pass RF, et al. The outcome of genital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992;326:663–67.

TABLE 16.4. SEQUELAE IN CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION ACCORDING TO TYPE OF MATERNAL INFECTION[a]

The exact means by which pregnant women acquire primary CMV is not known. Because CMV is not highly contagious, infection with the virus requires close contact with infected bodily secretions. CMV is sexually transmitted, and pregnant women may also be infected by household spread of CMV from young children, who often have a high prevalence of the virus (14). As noted by Yow (4), children attending day care centers have become a major source for parental transmission of CMV. From 25% to 80% of children attending day care centers acquire CMV, which they shed in their urine and saliva for up to 2 years (14,15 and 16). Clearly, these toddlers transmit CMV to their mothers and to other family members (14,15 and 16). Fifty percent of susceptible household members will seroconvert when CMV is introduced into the household (17). With increasing use of day care centers, CMV transmitted in this setting has become a major source of primary maternal CMV infection during pregnancy. Stagno et al. (6) reported that risk factors for primary CMV infection in pregnancy include (a) presence of young child in the home; (b) white race; (c) younger age; and (d) middle to upper income. These characteristics fit the women most likely to use day care centers. Adler (18) suggested that approximately 25% of serious congenital CMV infections (primary CMV) are attributable to the day care setting.

There are multiple potential sources of perinatal infection with CMV. Transplacental vertical transmission from mother to fetus has been confirmed. In addition, *in utero* infection may possibly be due to ascending infection across intact membranes from an infected cervix. The frequent presence of CMV in the cervix and birth canal is an obvious source for acquired neonatal CMV infection, similar to that seen with HSV. CMV has been isolated in breast milk. Stagno et al. (19) demonstrated that 70% of children of seropositive mothers excreting CMV in breast milk will acquire CMV (i.e., positive cultures) within 3 months of commencing breast-feeding). Another potential source of infection is sibling contact. However, as noted already, perinatal CMV is only a cause of neurologic sequelae in very-low-birthweight infants. Presumably this is due to immune system incompetence.

In general, primary maternal infection is viewed as potentially more dangerous for the fetus, but not all fetuses of mothers with primary CMV infection become infected (20,21). Hunter et al. (8) reported that 46% (17 of 37) of infants born to women with primary CMV infection were infected *in utero.* Only 2 (11%) of these 17 congenital infections were clinically detected in the nursery (8). Despite the high prevalence of CMV infection in pregnant women (documented by cervical excretion or viruria), infection in the mother is three to four times greater than that in neonates. Of more significance is the timing of infection in gestation. Manif et al. (21) showed that the more severely affected infants are those who acquire CMV infection in the first or second trimester of pregnancy. Those born to mothers with maternal infection after the third trimester were normal at birth but had positive cord serum for CMV IgM antibodies, suggesting “silent” congenital CMV infection. Stern and Tucker (20) showed that 50% of infants whose mothers developed a primary infection during pregnancy were excreting virus after delivery. Of the eight women who had reactivation of CMV infection during pregnancy, none of their infants were excreting virus after delivery. Stagno et al. (6) reported that primary CMV infection during pregnancy was associated with a 30% to 40% risk of intrauterine transmission. Adverse outcomes are more likely when infection occurs within the first 20 weeks of gestation (Table 16.5) (6). Recently Boppana et al. (22) demonstrated that the important determinants of CMV vertical transmission *in utero* were (a) higher levels

of maternal anti-GB antibody at delivery; (b) longer duration from seroconversion to peak levels anti-GB antibody; and (c) higher levels of anti-CMV IgM antibody at the first prenatal visit and at delivery. Thus, it appears that primary CMV infection during the first two trimesters presents a greater risk for fetal infection than does infection occurring in the third trimester.

	Gestational Age (Wk)			
Outcome	4–12	16–27	28–40	Total
Primary infection	33	10	26	69
Congenital infection	17 (51%)	6 (60%)	12 (46%)	35 (51%)
Symptomatic at birth	2 (12%)	1 (16%)	0	3 (8%)
Significant handicaps	5 (29%)	0	0	5 (13%)

Source: From Stagno S, Pass RF, Cloud G. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus and clinical outcome. JAMA 1986;256:1904–1908, with permission.

TABLE 16.5. PRIMARY CYTOMEGALOVIRUS INFECTION: EFFECT OF GESTATIONAL AGE ON TRANSMISSION *IN UTERO* AND DISEASE IN OFFSPRING

The public health impact of congenital CMV infection in the United States is immense (Table 16.6 and Fig. 16.3) (23). With an estimated 4 million births annually and an average rate of congenital CMV of 1%, there are more than 7,000 infants born each year who either die or develop significant neurologic sequelae due to congenital CMV.

Parameter	Estimated Figure
No. of livebirths per year	4,000,000
Rate of congenital infection	1%
No. of infected infants	40,000
No. of infants symptomatic at birth (10%)	4,000
No. with fatal disease (±25%)	1,000
No. with sequelae (90% of survivors)	2,700
No. of infants asymptomatic at birth (90%)	36,000
No. with late sequelae (10%)	3,600
Total no. with sequelae or fatal outcome	7,300

Source: From Stagno S. Cytomegalovirus. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn*. Philadelphia: WB Saunders, 1990:241–281, with permission.

TABLE 16.6. PUBLIC HEALTH IMPACT OF CONGENITAL CYTOMEGALOVIRUS INFECTION IN THE UNITED STATES

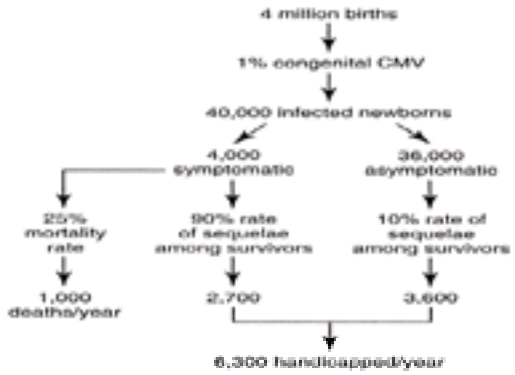


FIGURE 16.3. Public health impact of congenital cytomegalovirus infection in the United States.

The prognosis is poor for babies with clinically apparent disease at birth. The mortality in these infants is estimated to be as high as 20% to 30%, and 90% will have late complications (3). CNS and perceptual disabilities usually result in severe mental retardation. The major site for this chronic morbidity is the brain and perceptual organs, with resultant seizures, spastic diplegia, optic atrophy, blindness, and sensorineural deafness. With recent emphasis shifting from the obviously diseased infant, the major focus of interest is on the prognosis of the 90% of congenitally infected neonates who appear normal at birth. These children may not develop normally, as significant neurologic sequelae may become apparent with time. Long-term longitudinal follow-up studies have documented progressive sensorineural hearing loss and apparently subtle brain damage resulting in lowered intelligence quotient (IQ) and school-associated behavioral problems, which develop over several years after delivery of infants with subclinical CMV. The prevalence of CMV infection suggests that this agent may be a leading cause of deafness, a major contributor to school-related learning disabilities, and a significant public health problem (24).

Diagnosis

Clinical Manifestations

Maternal Infection.

More than 90% of maternal infections with CMV, primary or recurrent, are asymptomatic. Occasionally, CMV infection presents as a heterophil-negative mononucleosis syndrome with leukocytosis, with relative and absolute lymphocytosis, abnormal liver function test results, abrupt onset of spiking temperature, and constitutional symptoms such as malaise, myalgias, and chills. The mildness of the pharyngitis, minimal lymphadenopathy, and absence of hepatosplenomegaly and jaundice help to differentiate CMV from the infectious mononucleosis syndrome.

Neonatal Infection.

The spectrum of disease caused by CMV in the fetus and neonate is very broad. Of the congenitally infected infants, 90% are completely asymptomatic at birth. Clinically apparent disease occurs in 10% of infants with congenital CMV and ranges from isolated organ involvement to the classic multiorgan system disease. Approximately 50% of the symptomatic infants have the typical generalized pattern of the characteristic cytomegalic inclusion disease (3). In severely infected neonates, the clinical features include hepatosplenomegaly, jaundice, thrombocytopenia, purpura, microcephaly, deafness, chorioretinitis, optic atrophy, and cerebral calcifications (Table 16.7). The cerebral calcifications of CMV are characteristically periventricular in the subependymal region. A characteristic tetrad of findings has been described in infants who have survived fulminant clinically apparent CMV infection. These are (a) mental retardation, (b) chorioretinitis, (c) cerebral calcification, and (d) microcephaly or hydrocephaly. Such severe symptomatic CMV disease occurs in an estimated 1 in 10,000 to 1 in 20,000 newborns.

Abnormality	No. Positive/No. Examined
Petechiae	27/34 (79%)
Hepatosplenomegaly	25/34 (74%)
Jaundice	20/32 (63%)
Microcephaly	17/34 (50%)
Small for gestational age	14/34 (41%)
Prematurity	11/32 (34%)
Inguinal hernia	5/19 (26%)
Chorioretinitis	4/34 (12%)

Source: From Stagno S, Pass RF, Dworsky ME, et al. Congenital and perinatal cytomegalovirus infection. *Semin Perinatol* 1983;7:30–42, with permission.

TABLE 16.7. CLINICAL FINDINGS IN 34 NEWBORN INFANTS WITH SYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS INFECTION

The long-term prognosis for symptomatic congenital CMV infection is poor (25). The mortality rate is 20% to 30%, and more than 90% of the survivors develop significant neurologic sequelae (Table 16.8) (25). These sequelae include microcephaly, psychomotor retardation, neuromuscular disorder, unilateral and bilateral hearing loss, chorioretinitis, optic nerve atrophy, and dental defects.

Complication	% Occurrence	
	Symptomatic (n = 92)	Asymptomatic (n = 269)
Death	30	0
Microcephaly	48	4
Psychomotor retardation neuromuscular disorder	70	4
Hearing loss	61	5
Unilateral	30	64
Bilateral	70	36
Progressive	57	36
Chorioretinitis or optic atrophy	14	2
Dental defects	27	4
Total with one or more complications	92	6

Source: From Pass RF, Stagno S, Meyers GJ, et al. Outcome of symptomatic congenital CMV infection: results of long-term longitudinal follow-up. Pediatrics 1980;66:758–762, with permission.

TABLE 16.8. COMPLICATIONS IN PATIENTS WITH SYMPTOMATIC OR ASYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS INFECTION

Ninety percent of newborns with congenital (intrauterine acquired) CMV infection are asymptomatic. However, 5% to 15% of newborns with asymptomatic CMV infection at birth will go on to develop late sequelae (2,26,27) such as sensorineural hearing loss, subnormal intelligence, and behavioral problems.

Hanshaw et al. (26) screened 3,300 cord bloods for CMV-specific IgM and followed the positive infants for 4 to 6 years (Table 16.9). These authors demonstrated that CMV IgM–positive newborns were at significantly increased risk to have school failure, an IQ of less than 90, microcephaly, and sensorineural hearing loss (26). Similarly, the Alabama group reported on their 4-year follow-up of neonates with asymptomatic congenital infection and identified complications associated with asymptomatic congenital CMV infection (27). Approximately 2% developed microcephaly with various degrees of mental retardation and neuromuscular defects by age 2. An additional 1% and 7% developed chorioretinitis and sensorineural hearing loss, respectively.

	CMV IgM-Positive	Matched Controls	Random Controls
Predicted school failure	16/44	6/44	2/44
IQ <90	13/44	6/44	2/44
Microcephaly	7/43	2/44	2/43
Hearing loss	1/43	3/42	0/44
Chorioretinitis	1/44	0/44	0/44

CMV, cytomegalovirus; IgM, immunoglobulin M; IQ, intelligence quotient.
Source: From Hanshaw JB, Scheiner AP, Moxley AW, et al. School failure and deafness after "silent" congenital cytomegalovirus. N Engl J Med 1976;295:468–470, with permission.

TABLE 16.9. FOLLOW-UP STUDIES OF CMV-SPECIFIC IGM-POSITIVE NEONATES

Laboratory

Maternal Infection.

Because maternal infection is almost always asymptomatic, the diagnosis is rarely suspected or confirmed in pregnancy. Even when clinical disease occurs, it is generally mild, and CMV is usually overlooked as a diagnostic possibility.

Several reliable IgG antibody tests are available for CMV. These include indirect hemagglutination, enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody, and neutralization tests. Because approximately 40% of adults have antibody, a single positive result does not necessarily indicate recent or current infection.

Demonstration of seroconversion is the best documentation of primary infection. If infection has occurred within the previous 4 to 8 months, IgM-specific antibody can be detected in the serum. However, currently available IgM assays have not been evaluated on a widespread clinical basis (14). Moreover, IgM may remain positive for up to 18 months and in 10% of women with recurrent CMV, IgM can be detected.

Another way to establish the presence of CMV infection is by isolating the virus. Virus isolation does not differentiate primary and recurrent infections. On the other hand, diagnosis of asymptomatic recurrent CMV depends on viral isolation from urine or cervix, because no change in antibody level occurs in normal hosts with recurrent infection. CMV from swabs or urine may require 2 to 6 weeks before cytopathic effects of the virus are seen in tissue culture. Polymerase chain reaction (PCR) detection of CMV is available and provides a sensitive and specific diagnostic test for the presence of CMV.

Infections In Neonates.

A small percentage of clinically apparent infections in neonates are similar in presentation to other congenital infections, such as toxoplasmosis, rubella, syphilis, and herpes. The characteristic periventricular calcifications may be helpful in clinically differentiating congenital CMV infection from these other infections, but laboratory confirmation is necessary to document CMV infection. Although serology can be used as an aid in the diagnosis of congenital CMV infection, virus isolation is more sensitive and direct. As in adults, newer methods such as an indirect hemagglutination test, ELISA, and a fluorescent antibody test have replaced the CF test.

Most neonates with congenital CMV have antibody to CMV when tested with the newer methods. Approximately 80% of congenitally infected infants have IgM-specific antibody in the serum during the first few months of life. This test is rather sophisticated and available from only a few medical research laboratories.

Virus isolation is the best method available for documenting newborn CMV infection. Specimens can be taken from the urine, nasopharynx, conjunctiva, and spinal fluid.

PCR is also available.

Characteristic cytomegalic inclusions may be seen in tissues collected at autopsy or by biopsy, for example, of the kidney.

The laboratory abnormalities found in neonates with symptomatic congenital CMV infection are listed in Table 16.10 (25). Similar abnormalities can be detected in the *in utero* infected fetus and are included as part of the assessment for prenatal diagnosis of congenital CMV.

Test	No. Abnormal/ No. Tested	% Abnormal
Elevated cord IgM	21/25	84
Atypical lymphocytosis	8/10	80
Elevated SGOT level	14/18	78
Thrombocytopenia	17/28	61
Hyperbilirubinemia	19/31	61
Increased CSF protein	9/19	47

CMV, cytomegalovirus; IgM, immunoglobulin M; SGOT, serum glutamic-oxaliacetic transaminase; CSF, cerebrospinal fluid.
Source: From Pass RF, Stagno S, Meyers GJ, et al. Outcome of symptomatic congenital CMV infection: results of long-term longitudinal follow-up. *Pediatrics* 1980;66:758–762, with permission.

TABLE 16.10. LABORATORY ABNORMALITIES IN SYMPTOMATIC CONGENITAL CMV INFECTION

Prenatal Diagnosis

Recently, prenatal diagnosis of *in utero* acquired (congenital) CMV infection of the fetus has become available using ultrasound, amniocentesis, and cordocentesis (percutaneous umbilical cord sampling). On ultrasound, the most common findings include microcephaly; hydrocephalus; necrotic, cystic, or calcified lesions in the periventricular region of the brain, liver, or placenta; intrauterine growth retardation; oligohydramnios; ascites; pericardial or pleural effusion; hypoechogenic bowel; and hydrops.

Direct fetal sampling via fetoscopy (28) and cordocentesis (29) has detected elevated levels of anti-CMV IgM. Subsequent studies by Weiner and Grose (30), Hohlfeld et al. (31), and Lamey et al. (32) demonstrated that amniocentesis with culturing of amniotic fluid is an excellent method for detection of *in utero* CMV infection. With amniotic fluid culture, these authors correctly diagnosed all cases of congenital CMV infection. The accuracy of amniotic fluid cultures for CMV is not unexpected, because the fetal kidney is one of the major sites for CMV involvement. Weiner and Grose (30) recommended amniotic fluid culture for CMV in pregnant women with documented primary CMV infection or when ultrasonography suggests intrauterine growth retardation, hydrops, ascites, and CNS abnormalities.

Hohlfeld et al. (31) suggested that fetal blood sampling could provide additional

information about the fetal condition. Grossly abnormal laboratory findings such as severe thrombocytopenia, anemia, or signs of hepatic involvement were associated with a rapidly fatal outcome after birth (31). With cordocentesis for fetal blood sampling used to complement ultrasound and amniocentesis, assessment of *in utero* CMV infection includes specific and nonspecific tests for fetal CMV infection (Table 16.11). Recently, Donner et al. (33) reported that the combination of these tests resulted in antenatal diagnosis of CMV in 13 of 16 infected fetuses (sensitivity, 81%). Amniocentesis diagnosed 12 of 13 antenatally identified cases of CMV infection. Of these 12 cases, 4 had a negative result on the first amniocentesis before 20 weeks; 4 to 8 weeks later, the results of a second amniocentesis were positive. Thus, with a strong suspicion (i.e., documented maternal primary CMV) if the initial assessment is negative, the testing should be repeated 4 to 8 weeks later. Detection of CMV IgM antibody in fetal blood had a sensitivity of 69% (9 of 13 cases). Antsaklis et al. analyzed 42 pregnant women with primary CMV infection and reported that in 14 (33.3%) of pregnancies vertical transmission of CMV occurred (34). Positive amniotic fluid culture and positive PCR were present in 9 (64.3%) and 12 (78.6%) infected fetuses. Combining both tests diagnosed 12 of 14 infected fetuses (sensitivity 85.7%). Guerra et al. assessed the relationship of CMV viral load in amniotic fluid with fetal or neonatal outcome using PCR and quantitative PCR (35). CMV infection was noted in 16 (23%) fetuses and neonates, 5 of whom were symptomatic. Using quantitative PCR, these authors demonstrated that the presence of ^{3} 10^{5} genome equivalents predicted development of symptomatic infection. Most recently, Azam and co-workers assessed amnioncentesis, fetal blood sampling and serial ultrasounds in the prenatal diagnosis of CMV (36). nearly 23% (26 of 114) of fetuses were infected with prenatal diagnosis identifying 20 of these cases, resulting in a sensitivity of 77% and specificity of 100%. In this study, amniocentesis best diagnosed fetal infection while ultrasound examination and fetal blood sampling identified fetuses at risk for severe sequelae (36).

Amniocentesis
Virus isolation by culture (monoclonal antibody early AG13)
PCR
Fetal blood sampling (PUBS)
Indirect
CBC and platelet count
Liver function test (γ-glutamyltransferase)
Total IgM
CMV-specific IgM
Direct
Viral culture
Viral antigen
PCR

CMV, cytomegalovirus; PCR, polymerase chain reaction; IgM, immunoglobulin M; CBC, complete blood count; PUBS, percutaneous fetal blood sampling.

TABLE 16.11. DIAGNOSIS OF FETAL CMV INFECTION

Treatment

There is no specific treatment of CMV infection. In mothers with the infectious mononucleosis-like illness, treatment is symptomatic. No satisfactory therapy is available for congenital CMV infection. Attempts have been made to use antiviral

agents such as adenosine arabinoside and cytosine arabinoside for neonates with severe clinical infection, but these drugs are quite toxic. Further, although they temporarily suppress the excretion of CMV, virus shedding resumes when the drugs are stopped. Because of their toxicity, these antiviral agents are not used in asymptomatic CMV infection. Acyclovir is not effective against CMV, which unlike HSV, does not include its own thymidine kinase. Ganciclovir has recently been demonstrated to be effective in the treatment of CMV retinitis in HIV-infected patients (37). Another agent, foscarnet, is also approved for treatment of CMV retinitis. However, no published experience with these drugs in pregnancy or neonates is available to date.

The development of a CMV vaccine has been suggested as a means of preventing congenital CMV infection with its associated morbidity and mortality. Although CMV persists in the host even in the presence of high levels of specific antibody and the existing maternal antibody does not invariably protect against congenital infection, previous infection significantly reduces the risk of severe infection in the infant, particularly protecting against mortality, mental retardation, and other significant neurologic handicaps (13). These factors suggest that such an approach is likely to be successful. A live attenuated CMV vaccine (Towne strain) has been tested in volunteers and prospective renal transplant recipients (4). This vaccine elicits antibodies and cellular immune responses. Clearly, with molecular biology techniques, a recombinant vaccine can be developed for CMV. Use of such a vaccine could prevent nearly all of the neonatal deaths (n = 1,000) and approximately 90% of the severe neurologic sequelae associated with congenital CMV secondary to primary maternal infection that occur each year in the United States (based on data from Fowler et al. [13] comparing primary with recurrent maternal infection).

Screening And Counseling

Although reliable tests are available for detecting IgG class antibody to CMV in maternal serum, mass screening is not recommended (3,14). Such a screening program would be expensive, because detection of primary infection requires serial testing of women who are seronegative initially or testing for IgM. (As noted, tests for CMV-specific IgM have not been evaluated as a screening tool.) Then, even if primary infection is documented, present information does not allow straightforward decisions. Because most maternal infections are asymptomatic, the time in gestation of the infection is nearly always unknown. Prospective studies have shown that infections early in pregnancy are more likely to cause serious fetal injury than those late in pregnancy. Once maternal primary CMV infection has been documented, a combination of ultrasound, amniocentesis, and fetal blood sampling is necessary to identify the 30% to 40% of fetuses infected with CMV. A major limitation of a screening program is that many cases of congenital infection occur in immune women. Because there is no marker to detect these at-risk fetuses, all of these cases would be missed by a screening program.

Stagno and Whitley (3) conclude that “there is inadequate information to serve as a basis for recommendations regarding termination of pregnancy after a primary CMV infection. Similarly, there is no information regarding how long conception should be delayed after primary infection.” Pass et al. (14) note that “since the most likely outcome of pregnancy complicated by maternal CMV infection is a normal infant, the well-informed patient—in our experience—will usually not choose to terminate the

pregnancy.”

Because large quantities of CMV are excreted by infected neonates, it has been suggested that pregnant pediatric health care workers might be at high risk of developing CMV infection. However, Dworsky et al. (38) recently reported that the annual primary CMV infection rate (as determined by seroconversion) was no higher among pediatric house staff (2.7%) and pediatric nursing staff (3.3%) than it was among young women in the community (2.5% during pregnancy and 5.5% between pregnancies). The higher than expected rate of conversion between pregnancies suggests that exposure to young infants by family or other social exposure may be the most important factor in horizontal transmission. Pass et al. (14) showed that in several families, toddlers were the most likely source of CMV for both the mother and the fetus or infant. The toddler acquired the CMV in a day care center. As a result, the CDC currently recommends that day care workers be counseled regarding risk and instructed in careful, frequent hand washing. Use of gloves to handle material contaminated with body fluids is also useful. Seronegative workers may be offered the option of working with older children.

A metaanalysis of primary CMV infection in pediatric nurses has been performed (39). These authors identified six controlled studies performed to evaluate the risk of CMV infection among pediatric nurses (37,38,40,41,42,43 and 44). The pooled risk ratio for CMV infection (using cumulative incidence data) was statistically significant (risk ratio, 2.7; 95% confidence interval [CI], 1.33–5.52). However, person-year analysis only demonstrated a trend, which did not reach statistical significance (risk ratio, 1.8; 95% CI, 0.88–3.55). They concluded that in studies published before widespread adoption of universal precautions, pediatric nurses may have been at increased risk for CMV infection because of occupational exposure. However, inadequate design and sample size prevented a definite conclusion (39). More recently, Balcarek et al. (44) evaluated CMV infection risk in employees of a children's hospital. Of the 300 workers who initially were seronegative and followed, 13 seroconverted over a mean follow-up interval of 1.96 years, 2.2% per year. There was no statistically significant difference in the incidence of CMV infection by job type, number of hours per week of patient contact, or nursing unit. This incidence of CMV was similar to that expected in the general population (45). Standard infection control measures for handling potentially contaminated material in pediatric units would seem to provide sufficient protection from CMV infection. Further, other isolation measures in infants known to have CMV infection would be “useless or even dangerous” (3,38).

Hepatitis

Acute viral hepatitis is a systemic infection predominately affecting the liver. Distinct hepatotropic viral agents cause hepatitis types A, B, C (which was formerly known as non-A, non-B hepatitis), D, and E. Other transmissible agents causing secondary hepatitis include CMV, Epstein-Barr virus, varicella-zoster (VZ) virus, coxsackievirus B, HSV, and rubella virus. The major impact of hepatitis on the fetus and neonate relates to hepatitis B and hepatitis C. These viruses are discussed fully in Chapter 9 (Hepatitis).

Varicella-Zoster Infection

VZ virus is a member of the herpesvirus group. Similar to other members of the

herpesvirus group, VZ is a DNA virus and exhibits viral latency (1). Initial (primary) infection with VZ virus results in varicella (chickenpox). This common childhood disease is usually marked by typical skin lesions, which progress from macules and papules to vesicles that occur in successive crops and evolve into pustules that form crusts and scabs (2). A highly contagious disorder, it is acquired by most persons in the United States before reproductive age and is generally self-limited. Among adults who contract the disease, constitutional and pulmonary symptoms may be more severe. Zoster (shingles) is the result of reactivation of the latent virus. It generally occurs in the older adult population or in immunocompromised patients. Characteristically, zoster presents as painful vesicular lesions that occur in a pattern of distribution that follows segmental dermatomes. Availability of the varicella vaccine in the United States has led to a dramatic decrease in new cases of varicella (3).

This discussion focuses on the effects of VZ virus in pregnancy, the management and prevention of VZ infections during the perinatal period, and the possibly increased severity of the infection in pregnancy. Two major problems exist when VZ infection occurs in pregnancy. First, the infection itself poses a risk for significant morbidity and mortality for mother and neonate. Second, VZ virus has a teratogenic effect, and infection early in pregnancy may result in congenital anomalies.

Epidemiology

In 1998, more than 82,000 cases of chickenpox were reported in the United States (3), and this disease was third after chlamydia and gonorrhea as the most frequently reported infectious disease in the United States (3). Because of extensive underreporting, it has been estimated that 2 to 3 million cases of chickenpox occur annually in the United States (4,5 and 6). VZ is endemic in the United States and is extremely contagious; more than 90% of the population has been infected before adulthood (4). Consequently, chickenpox is uncommon among women of childbearing age and thus is uncommon in pregnancy. In the Collaborative Perinatal Research Study's prospective analysis of 30,059 pregnancies, 20 VZ infections were diagnosed, of which 14 were confirmed; thus, at a minimum, there were 5 VZ cases out of every 10,000 pregnancies (7). Balducci et al. (8) recently estimated the incidence of varicella in pregnancy to be 0.7 per 1,000 patients.

Clinical Presentation

VZ virus is highly contagious. It is spread by respiratory droplets and close personal contact. The incubation period of varicella ranges from 10 to 20 days but usually is 13 to 17 days. In children, fever and rash occur simultaneously, whereas in adults, fever and generalized malaise precede the rash by several days. Characteristically, the rash begins on the face and scalp and spreads to the trunk. The extremities tend to be minimally involved. Skin lesions begin as macules, then progress to a vesicular stage followed by pustules, crusts, and scabs. Itching is a common and prominent feature of the disease. For 2 to 5 days, new crops of lesions occur, and the various stages (i.e., vesicles, pustules, and scabs) are present simultaneously. Patients are contagious from 1 to 2 days before the onset of rash until the lesions have dried and become crusted.

The most common complication of chickenpox is secondary bacterial infection of the skin lesions (2). Rarely, encephalitis, meningitis, myocarditis, glomerulonephritis, and arthritis occur. The most serious complication of chickenpox is varicella pneumonia.

It occurs in about 5% to 10% of adults with chickenpox (and in a much smaller percentage of children) and is associated with a significant mortality risk.

Varicella pneumonia develops several days after onset of the rash. The severity of varicella pneumonia ranges from a mild illness to severe life-threatening disease characterized by cough, tachypnea, dyspnea, hemoptysis, chest pain, and cyanosis. On radiographic examination, the chest x-ray demonstrates diffuse, nodular peribronchial infiltrates, which in severe cases can progress to adult respiratory distress syndrome (Fig. 16.4).

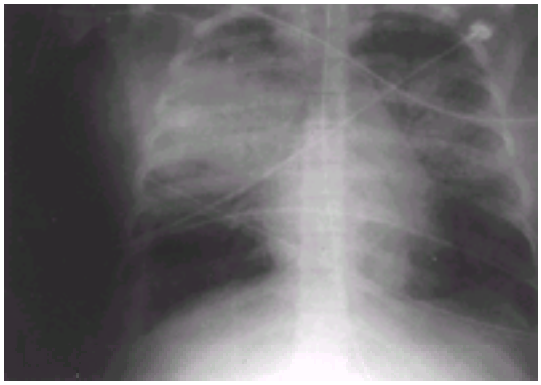


FIGURE 16.4. Chest x-ray of patient with varicella pneumonia during pregnancy.

Varicella In The Mother

Varicella is an unusual infection among adults and probably occurs with no greater frequency among pregnant women. In the past, pregnant women were believed to be at greater risk of developing severe or fatal varicella than were nonpregnant adults. However, the current consensus holds that although adults are at increased risk of developing varicella pneumonia, this risk is no greater among pregnant women (4,9,10). Recently, in a review of the literature on varicella pneumonia in pregnancy, Gershan (2) reported that among 198 cases of chickenpox in pregnant women, 57 (28%) developed varicella pneumonia. All 16 deaths occurred in the group with pneumonia, for a pneumonia mortality rate of 28% (overall mortality rate for varicella was 10%) (Table 16.12). This results in 14 (31%) deaths among 45 cases of pneumonia. Thus, it seems clear that uncomplicated chickenpox poses no severe risk to the pregnant woman. Although pneumonia (in the past) was associated with a significant mortality rate, pneumonia is an uncommon complication, and our current ability to manage severe respiratory distress and failure is much enhanced. Moreover, acyclovir in high doses is effective against VZ (6). While the mortality rate for varicella pneumonia during pregnancy has improved since the introduction of high dose acyclovir (1985), mortality remains a concern.

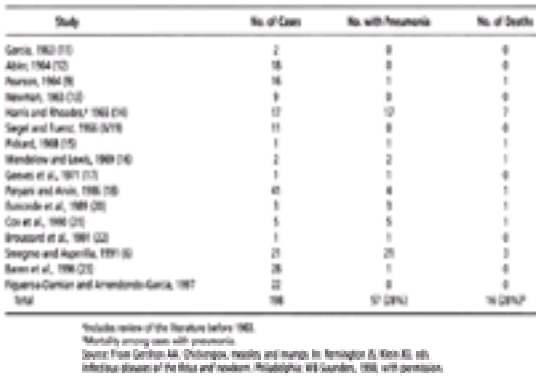


TABLE 16.12. MATERNAL MORTALITY ASSOCIATED WITH VARICELLA DURING PREGNANCY

The clinician must maintain a high index of suspicion that pneumonia may complicate varicella in pregnant women. Pulmonary symptoms begin on the second to sixth day after appearance of the rash and usually consist of a mild nonproductive cough. If the disease is more severe, there may be pleuritic chest pain, hemoptysis, dyspnea, and frank cyanosis. Physical examination reveals fever, rales, and wheezes. The chest x-ray characteristically reveals a diffuse nodular or miliary pattern, particularly in the perihilar regions. With varicella in pregnancy, the patient should be warned to contact the physician immediately if even mild pulmonary symptoms develop. Hospitalization with full respiratory support, if necessary, should then be made available.

Smego and Asperilla (6) described their experience with the use of acyclovir in the management of severe varicella (i.e., pneumonia) during pregnancy. They reported on 21 cases, of which 12 required intubation and mechanical ventilation for severe pneumonia. The mortality rate was 14% (three deaths), with all deaths occurring in the third trimester. The recommended dosage of acyclovir for treatment of severe varicella is 10 to 15 mg per kilogram of body weight intravenously three times daily for 7 days. The equivalent oral dosage is 800 mg five times per day. These authors noted no adverse effects due to acyclovir (6).

Paryani and Arvin (18) reported the consequences of maternal varicella in 43 pregnancies. Nine women (21%) developed associated morbidity. Four women (9%) developed varicella pneumonia, and one of these women died (at 6 months into the pregnancy). Another required ventilator support. Premature labor developed in 4 (10%) of 42 and premature delivery in 2 (5%) of 42. On the other hand, morbidity was rare when herpes zoster occurred (18). In 13 (93%) of 14 cases, no complications occurred. A single patient developed cutaneous disseminated disease (18).

Because varicella infection in pregnancy is associated with significant morbidity and mortality, prevention of varicella among susceptible exposed patients is paramount. For a pregnant woman with exposure to varicella, infection is very likely if she is not immune. As recently pointed out by McGregor et al. (25), most pregnant women (12 of 17; 71%) with a negative history of chickenpox had detectable antibody. Further,

of those with indeterminate histories, an even greater percentage of pregnant women were immune (18 of 20; 90%). Thus, it is appropriate and cost-effective in the face of maternal exposure to test for maternal antibody by any of the following methods: fluorescent antibody to membrane antigen, ELISA, immune adherence hemagglutination, and the enhanced neutralization test (20) (Fig. 16.5).

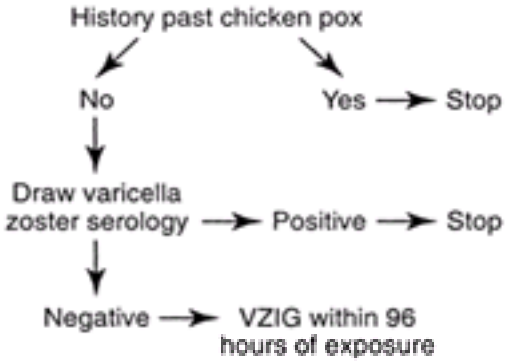


FIGURE 16.5. Protocol for management of pregnant women exposed to varicella.

Then, in susceptible women, varicella-zoster immune globulin (VZIG) may be given (18,19). When given intramuscularly within 96 hours of exposure, it is likely that VZIG ameliorates the course of the maternal disease, as it does in children. There is no certainty, however, that passive immunization prevents fetal infection. The recommended dose of VZIG is 125 units per 10 kg of body weight up to a maximum of 625 units (five vials) intramuscularly. The average pregnant woman requires the maximum dose, at a cost of approximately $625.

Effects Of Varicella In Early Pregnancy

Maternal VZ infection has been reported to result in spontaneous abortion, stillbirth, and congenital anomalies (19,26). Congenital anomalies due to varicella in early pregnancy were not recognized until LaForet and Lynch (27) (in 1947) reported the birth of an infant, exposed to VZ virus during the first trimester, who had limb hypoplasia, cicatricial skin lesions, atrophic digits, bilateral cortical atrophy, severe psychomotor retardation, and growth retardation. It is now appreciated that maternal varicella infection in the first trimester of pregnancy can produce a congenital varicella syndrome, which consists of cutaneous scars, limb hypoplasia, rudimentary digits, ocular abnormalities (e.g., optic atrophy, microphthalmia, and cataracts), cerebral cortical atrophy, mental retardation, and growth retardation. Because both gestational varicella and the reported cases of varicella congenital syndrome are uncommon, the risk of a fetus developing congenital anomalies if the mother acquired chickenpox during the first trimester has been quantitated only recently. The risk of developing the congenital varicella syndrome after exposure in the first trimester is reviewed in Table 16.13. Overall, only 1% of infants exposed to VZ virus during the first trimester developed stigmata of congenital varicella, with a range of 0% to 9%. Recently Pastuszak et al. (25) studied 120 women with varicella in pregnancy; 106 had varicella during the first 20 weeks of gestation. When the

authors controlled for elective terminations and spontaneous abortions, congenital defects occurred in four infants (1.2%) in the varicella group (95% CI, 0–2.4%). Enders et al. (26) recently reported a large prospective study in Germany and the United Kingdom of 1,373 women who had varicella before 36 weeks of gestation. Nine cases of congenital varicella syndrome were identified, for a risk rate of 1%. The highest risk (2.0%) was noted between 13 and 20 weeks of gestation (7 of 351 pregnancies; 95% CI, 0.8–4.1%). Before 13 weeks, only 2 (0.4%) of 472 pregnancies (95% CI, 0.05–1.5%) were identified.

Study	No. of Infants Exposed	No. of Infants with Congenital Varicella-Zoster Virus (%)
Siegel (28)	27	2 (7.4)
Paryani and Arvin (29)	11	1 (9)
Enders (26)	23	0
Balducci et al. (6)	35	0
Pastuszak et al. (30)	49	1 (2)
Enders et al. (31)	472	2 (0.4)
Total	617	6 (1)

TABLE 16.13. RISK OF CONGENITAL VARICELLA-ZOSTER SYNDROME WITH ACUTE MATERNAL VARICELLA-ZOSTER INFECTION DURING THE FIRST TRIMESTER OF PREGNANCY

Higa et al. (33) suggested that many of the congenital malformations related to VZ virus may not be caused by acute varicella in the fetus but are the result of sequelae of recurrent herpes zoster in the fetus. In particular, recurrent herpes zoster infection would explain the cutaneous and limb abnormalities that follow nerve distributions. On the other hand, acute varicella is responsible for the CNS and neurologic lesions present in the congenital varicella syndrome. The frequency of clinical findings in infants with congenital varicella syndrome is presented in Table 16.14. Cicatricial skin lesions, eye abnormalities, and hypoplastic limb are the most common findings. Nearly one fourth of the affected infants died. Although the risk of congenital varicella syndrome is low, administration of VZIG to pregnant women without evidence of previous varicella as soon as possible (but within 96 hours of exposure) is recommended, because this may protect the fetus during the viremia (see the previous section). Once the mother has the rash, there would be no reason to administer VZIG, as viremia will have already occurred. VZIG is prepared from donors with high antibody titers to VZ virus.

Defect	No. of Cases (%)
Cicatricial skin lesions	26 (70)
Eye abnormalities	23 (62)
Cataract	9 (24)
Chorioretinitis	10 (27)
Microophthalmia	10 (27)
Hypoplastic limb	17 (46)
Cortical atrophy/mental retardation	11 (30)
Early death	9 (24)

Source: From Gershon AA. Chicken pox, measles, and mumps. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn*. Philadelphia: WB Saunders, 1990:395–445, with permission.

TABLE 16.14. CLINICAL DATA IN INFANTS WITH DEVELOPMENTAL DEFECTS BORN TO 37 WOMEN WITH VARICELLA-ZOSTER INFECTIONS DURING EARLY PREGNANCY

As with other perinatal infections, ultrasonography, amniocentesis, chorionic villus biopsy, and cordocentesis have been proposed as techniques for diagnosing *in utero* varicella infection (32,34,35 and 36). Although virus-specific IgM antibody can be detected in cord blood by 19 to 22 weeks of gestation and VZ virus can be recovered from amniotic fluid and identified by *in situ* hybridization in placental tissue, detection of either antibody or virus does not provide information about the severity of fetal infection. Ultrasound assessment appears to be the best method available for assessing the severity of fetal involvement with varicella infection. Pretorius et al. (36) reported ultrasound findings in 37 cases with maternal varicella infection in early pregnancy and that all five fetuses with sonographic abnormalities on sonography had varicella embryopathy at postdelivery examination or autopsy. All sonographic abnormalities were observed before 20 weeks. These abnormalities included polyhydramnios, hydrops fetalis, and multiple hypoechogenic foci within the liver (36). Ultrasound has also been successful in identifying abnormal limb development. These authors noted that 14 of 17 fetuses with hypoplastic limbs also either had brain damage or died in early infancy. More recently, Mouley et al. utilized PCR of amniotic fluid for pernatal diagnosis of V-1 infection in 107 pregnant women with varicella prior to 24 weeks gestation (32). Nine (8.4%) of specimens were positive by PCR versus 2 (1.8%) by culture. The reported incidence of congenital varicella-zoster was 3 (2.8%); all were PCR positive and 2 had abnormal sonographic findings at 21–22 weeks (32). The third infant had bilateral microopthalmia in the face of a normal ultrasound at 24 weeks (32).

Varicella In The Newborn

P>Acquisition of maternal antibody usually protects the fetus. However, if an infant is born after the maternal viremia but before the mother has developed an antibody response, the fetus is at high risk for life-threatening neonatal varicella infection. Infants at risk are those whose mothers contract varicella within 2 days of birth or within the first 5 days after delivery (37,38). Congenital varicella infection has been reported in 10% to 20% of full-term infants born to mothers with varicella within 4 to 5 days of delivery, and the case fatality rate was 20% to 30% (4,37). Infants born 5 or more days after the onset of maternal illness developed either mild varicella or no

infection at all.

Management of varicella in the newborn should focus on prevention. Ideally, delivery should be delayed until 5 to 7 days after the onset of maternal varicella. This will allow transfer of protective IgG antibody from the mother to the fetus. However, if delay is not possible, then the neonate should receive VZIG passive immunization as soon as possible after delivery.

VZIG modifies or prevents varicella in normal children, and Brunell (10,39) recommended its use in preventing severe neonatal varicella. Thus, infants at risk (those born to mothers who develop varicella between 5 days before and 2 days after delivery) should receive VZIG as passive immunization. The dose is 125 units. Recently, Miller et al. (38) reported on the outcome of 281 newborns whose mothers had chickenpox during the perinatal period. All infants had received VZIG shortly after birth. However, 169 of the children (60%) were noted to be infected—134 (48%) with chickenpox and 35 (13%) without clinical features. Although VZIG did not prevent neonatal varicella, it did prevent fatal outcome. The authors concluded that VZIG is still indicated for newborn infants whose mothers have chickenpox within 7 days before or after delivery. This differs from the recommendation of 5 days before delivery in the United States.

The CDC has published guidelines for the prevention of varicella (40). A live attenuated virus vaccine (Varivax) has been approved in the United States since 1995. See Chapter 25 for a detailed discussion of varicella vaccine. Because Varivax is a live attenuated virus it is recommended that pregnant women nor women attempting to conceive not receive varicella vaccine (40). A Pregnancy Registry for Varivas has been established and from May 1995 through December 1998 there were 371 women vaccinated within 3 months before or during pregnancy prospectively reported. There were zero cases of congenital varicella reported (95% C.I. 0.0–0.01). This finding plus the 1% rate of congenital varicella resulting from mild varicella virus infection resulted in the recommendation that exposure to varicells is not an indication for pregnancy termination (40). Also, because the vaccine virus is not transmissible, presence of a pregnant woman in a household is not a contraindication for vaccination of household members (40).

Effect Of Zoster On Pregnancy

Herpes zoster is caused by the same virus that causes varicella. It occurs very rarely in pregnancy. Because it is a reactivation of latent VZ virus and maternal antibodies are present in normal healthy women, zoster poses no threat to the fetus or neonate (18).

Measles (Rubeola)

Rubeola is an acute illness that most commonly occurs in childhood. It is the most communicable of the childhood exanthems. Rubeola is characterized by fever, coryza, conjunctivitis, cough, and a generalized maculopapular rash that usually appears 1 to 2 days after the pathognomonic Koplik spots in the oral cavity. The rubeola virus is a paramyxovirus that contains RNA as its nuclear protein.

Epidemiology

The virus is spread chiefly by droplets expectorated by an infected person and gains access to susceptible people via the nose, oropharynx, and conjunctival mucosa. The incubation time is between 10 and 14 days. Measles is most communicable during the prodrome and catarrhal stages of the infection. Approximately three fourths of exposed susceptible contacts acquire rubeola.

Before the availability of live measles vaccines, epidemics of measles occurred at intervals of 2 to 3 years in the United States. The use of attenuated measles vaccine since 1963 has had a major impact in decreasing the number of measles cases in the United States (1).

Measles occurs less frequently during pregnancy than chickenpox or mumps. Before the introduction of the measles vaccine, there were 0.4 to 0.6 cases of measles per 10,000 pregnancies. This figure is probably even lower since the measles vaccine was introduced.

Clinical Manifestations

The prodrome of fever and malaise begins 10 to 11 days postexposure and is followed within 24 hours by coryza, sneezing, conjunctivitis, and cough. This catarrhal phase is exacerbated over the next several days, and a marked conjunctivitis and photophobia occur. The pathognomonic Koplik spots appear at the end of the prodrome. These are tiny, granular, slightly raised white lesions surrounded by a halo of erythema, which are located on the lateral buccal mucosa. The rash appears 12 to 14 days after exposure. It begins on the head and neck, particularly postauricularly, and subsequently the maculopapular rash spreads to the trunk, upper extremities, and finally the lower extremities.

The respiratory tract is the most frequent site for complications of measles. Otitis media and croup are frequent occurrences, but bacterial pneumonia is the complication most frequently associated with mortality. The most common bacterial organisms involved in rubeola pneumonia are *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Streptococcus pyogenes.* Encephalitis, a less common but serious complication, is estimated to occur with a frequency of 1 per 1,000 cases of measles. Other complications of measles include thrombocytopenic purpura, myocarditis, and subacute sclerosing panencephalitis, which is a progressive neurologic disease associated with chronic rubeola infection of the CNS.

Maternal Effects Of Measles

It is unclear whether pregnant women with measles are at greater risk for serious complications and death than nonpregnant adults. More recent studies in the United States and Australia have noted that measles in pregnant women is only rarely associated with pneumonia or other complications (2).

Fetal Effects Of Measles

Sever et al. (2) summarized the results of reports in the literature concerning measles in pregnancy, suggesting that there is an increased rate of prematurity in pregnancies complicated by measles, particularly when the disease occurs late in gestation. However, no clear evidence suggests that maternal measles is associated with an increased risk of spontaneous abortion.

Because of the rarity of measles in pregnancy, no statement can be made regarding the teratogenic potential of gestational measles for the fetus. No particular constellation of abnormalities has been found among the sporadic instances of congenital defects reported in association with maternal measles (3). In general, if there is any increased risk of malformations after measles, the risk is small.

Perinatal Measles

Measles that becomes clinically apparent in the first 10 days of life is considered transplacental in origin (i.e., congenital), whereas those cases occurring at 14 days or later are acquired postnatally. Postnatally acquired measles is usually associated with a mild course. Congenital measles includes cases in which the disease is present at birth or infection acquired *in utero* appears during the first 10 days of life. The spectrum of illness in congenital measles varies from a mild illness to a rapidly fatal disease. However, maternal measles immediately before delivery does not involve the fetus and neonate commonly.

Diagnosis

In general, the diagnosis of measles relies on a history of recent exposure and the typical clinical presentation of the disease. However, the diagnosis is more difficult during the prodrome (when the illness is most communicable) or when illness and the exanthema are attenuated by passively acquired measles antibodies. Included in the differential diagnosis are (a) drug eruptions and allergies, (b) rubella, (c) scarlet fever, (d) meningococcemia, (e) roseola, (f) Rocky Mountain spotted fever, (g) toxoplasmosis, (h) enterovirus, and (i) infectious mononucleosis.

Treatment And Prevention

The treatment of uncomplicated measles is symptomatic. When otitis media or pneumonia develops, appropriate antibiotic therapy should be instituted on the basis of a Gram stain and culture.

Passive immunization is recommended for the prevention of measles in susceptible exposed pregnant women, neonates, and their contacts in the delivery room or nursery. Immune serum globulin (ISG) in a dose of 0.25 mL per kilogram of body weight administered within 6 days after exposure may prevent or at least modify the infection (4,5). Children born to women who have measles in the last week of pregnancy or the first week postpartum should be given ISG as soon as possible in a dose of 0.25 mL/kg (4).

Measles, rubella, and mumps vaccines are available as monovalent measles vaccine, monovalent rubella, monovalent mumps, or in various combinations. Each dose of combined or monovalent vaccines contains human albumin, neomycin, sorbitol, and hydrolyzed gelatin. Live measles vaccine and live mumps vaccines are produced in chick embryo cell culture. Live measles vaccine, as a component of measles and rubella or MMR vaccines, should not be given in pregnancy or within 3 months of conception. Women who are given monovalent measles vaccine should not become pregnant within 30 days. Although no evidence exists to substantiate a risk of birth defects, these precautions are based on the theoretical risk of giving a live vaccine in early pregnancy (4).

Mumps

Mumps is an acute generalized infection with a predilection for the parotid and salivary glands, but that also may affect the brain, pancreas, and gonads. There is no associated rash. The mumps virus is a member of the paramyxovirus family and is thus an RNA virus.

Epidemiology

Mumps virus is transmitted by saliva and droplet contamination. The virus has been recovered from saliva and respiratory secretions from 7 days before the onset of parotitis until 9 days afterward. The usual incubation period is 14 to 18 days.

Mumps is primarily a disease of childhood, and only 10% of cases occur after the age of 15. Many adults are immune as a result of clinical or subclinical infection (one third of cases). However, mumps is much less contagious than measles or chickenpox, and even among susceptible subjects exposed to household members, the attack rate is low. Mumps occurs more frequently in pregnant women than does measles or chickenpox. The incidence in prospective studies has been variously reported as 0.8 to 10 cases per 10,000 pregnancies (1).

Clinical Manifestations

The prodrome of mumps consists of fever, malaise, myalgia, and anorexia. Parotitis occurs within 24 hours and is characterized by a swollen and tender parotid gland. The orifice of the Stensen duct is usually red and swollen. In most cases, parotitis is bilateral. The submaxillary glands are involved less often and almost never without parotid gland involvement. The sublingual glands are rarely affected. Mumps is generally a self-limited and complication-free disease. However, it can be a significant cause of morbidity.

Orchitis occurs in about 20% of postpubertal men and is the most common manifestation other than parotitis in this group. Oophoritis is far less common. The most common neurologic complication of mumps is aseptic meningitis. However, the course of mumps-associated aseptic meningitis is almost always benign and self-limited. In addition, mumps may cause pancreatitis, mastitis, thyroiditis, myocarditis, nephritis, or arthritis.

Maternal Effects Of Mumps

Mumps in pregnancy is generally benign and no more severe than in nonpregnant patients. Aseptic meningitis in pregnant patients is neither more frequent nor more severe. Mortality in association with mumps is extremely rare in both pregnant and nonpregnant women.

Fetal Effects Of Mumps

Retrospective studies have suggested that mumps during the first trimester of pregnancy is associated with a twofold increase in the incidence of spontaneous abortion (2). No significant association between maternal mumps infection and prematurity, intrauterine growth retardation, or perinatal mortality has been demonstrated. Mumps infection in pregnancy is not associated with congenital abnormalities (3).

Diagnosis

The diagnosis of mumps is usually made on clinical grounds. When there is acute bilateral painful parotitis with a history of recent exposure, the diagnosis is straightforward. It may be more difficult when disease is unilateral or confined to organs other than the parotid gland. In these cases, diagnosis depends on virus isolation or more usually by demonstration of a rising CF, HI, or neutralizing antibody titer in paired acute and convalescent serum.

Treatment

The treatment of mumps is symptomatic in both pregnant and nonpregnant patients. Analgesics, bed rest, and application of cold or hot compresses to the parotids are useful. Maternal mumps is not an indication for termination of pregnancy.

Prevention

The live attenuated mumps virus vaccine has been effective in preventing primary mumps. In susceptible subjects, 95% develop antibodies without clinically adverse reactions. The duration of protection afforded by immunization is not known. Immunization with the live mumps virus vaccine in pregnancy is contraindicated on the theoretical grounds that the developing fetus might be harmed. Although the risk to the fetus seems negligible, the innocuous nature of mumps in pregnancy suggests that any risk from vaccination in pregnancy is unwarranted.

Influenza

Influenza is an epidemic disease that has been known since antiquity. The influenza viruses are myxoviruses. Three antigenically different influenza viruses have been identified (1). Type A influenza is responsible for most epidemics and is associated with severe cases. Less frequently, type B is involved in epidemics, but it tends to cause milder clinical disease. The third, type C, is the least frequent.

Epidemiology

Both the frequency and severity of influenza epidemics have been related to antigenic changes in the virus (1). The major antigenic changes that occur at 10- to 30-year intervals are associated with severe infection; the minor antigenic changes that occur annually are not.

Two major pandemics with influenza have occurred in this century. The pandemic of 1918 was responsible for 20 million deaths worldwide (2). More recently, the Asian influenza pandemic of 1957 to 1958 caused considerable morbidity and mortality. Epidemics of influenza occur nearly every year during the winter months and are responsible for substantial morbidity and mortality in the United States, averaging approximately 114,000 hospitalizations and 20,000 deaths annually (3,4).

Clinical Presentation

The incubation type for influenza is 1 to 4 days. Influenza presents clinically with an abrupt onset of a respiratory infection associated with fever, malaise, myalgias, and headache. The severity of the disease varies from mild to severe with pneumonia present. The major portion of the clinical disease lasts, on average, 3 days.

Definitive diagnosis is made by virus isolation from throat washings during the acute illness or by serologic confirmation of a fourfold rise in antibody with paired acute convalescent serum. Either CF tests or HI tests may be done.

Maternal Effects Of Influenza

The major concern during pregnancy is the increased likelihood of life-threatening pneumonia as a complication of influenza among pregnant women. Reports from the epidemics of 1918, as well as from 1957, all indicate that pregnant women were disproportionately represented among individuals dying of influenza. The maternal mortality rate associated with influenza during the 1918 pandemic was approximately 30% (5,6). In 1919, Harris (6) reported that although the overall maternal mortality rate was 27%, in cases complicated by pneumonia, the mortality rate rose to 50%. Finland (7) noted that during the 1918 pandemic, the worldwide mortality rate was 10% in the general population, but that in some areas, the mortality rate in pregnant women was 80%. During the 1957 pandemic, in Minnesota, 50% of all deaths from Asian influenza among women occurred during pregnancy (8). It is not clear that pregnant women are more likely to develop influenza or that they are more likely to develop influenza pneumonia. However, if influenza pneumonia develops in pregnancy, it appears to be more severe. Deaths among pregnant women with influenza may result not only from secondary bacterial infection (such as with *S. aureus, S. pneumoniae,* or *Klebsiella* sp), but also from primary influenza pneumonia without bacterial superinfection.

Fetal Effects Of Influenza

The effect of influenza on rates of abortion, prematurity, and congenital anomalies is difficult to determine because the evidence is contradictory. In part, confusion may arise from variations of the virus itself from epidemic to epidemic and from lack of

well-controlled studies. Studies that did not include serologic confirmation of influenza infection have noted an increased risk for developmental anomalies in pregnancies with a history of influenza. In 1955, Coffey and Jessup (9) (in Ireland) noted that women who gave birth to infants with malformations (neural tube defects primarily) were more likely to have had a history of influenza during pregnancy (18.4%) than mothers delivering healthy babies (3.6%). In a subsequent prospective study, these investigators reported that the malformation rate was more than doubled in pregnancies with a history of influenza at the time of the 1957 Asian flu pandemic (10). Similarly, Doll et al. (11) (in Scotland) noted that congenital anomalies occurred at a higher rate among infants born to women with histories of influenza infection during pregnancy. Hakosalo and Saxen (12) confirmed this association among Finnish women. However, studies using serologic confirmation of influenza infection were not used. Hardy et al. (13) noted a 5.3% incidence of congenital anomalies among women infected during the first trimester; cardiac anomalies were the most common. Griffiths et al. (14) also noted an increase in anomalies, but they all occurred in pregnancies with influenza infection in the second and third trimesters. Wilson et al. (15) noted no increase in anomalies associated with influenza infection in early pregnancy. Similarly, neither the Collaborative Perinatal Research Study (16) nor the study by Brown (17) revealed any association between maternal influenza infection and congenital anomalies among offspring. In summary, most women who have influenza in pregnancy have normal outcomes, and there seems to be little influence on congenital anomalies, intrauterine growth, prematurity, or stillbirth.

Management And Prevention

Management of the uncomplicated pregnant woman with influenza consists of symptomatic relief (1), with bed rest, analgesia, liberal fluid intake, and fever control with acetaminophen. The physician must be alerted to the development of pneumonia. If pneumonia occurs in pregnant women with influenza, prompt hospitalization is indicated and broad-spectrum antibiotic coverage (i.e., ceftriakone) for bacterial superinfection pneumonia is required. Respirator support may be needed if there are problems with adequate oxygenation, with retention of carbon dioxide, or with excessively labored breathing.

Use of amantadine, which blocks the replication of influenza A virus, has been efficacious in nonpregnant patients, to prevent symptoms, shorten the clinical course, and improve pulmonary function (18). However, the drug has been associated with teratogenic effects in animals and is not recommended for use in pregnancy (19).

In years of epidemics, it is generally considered advisable to vaccinate pregnant women. During the 1977 Swine flu vaccination program, however, pregnancy was not considered among the high-risk conditions, such as rheumatic heart and chronic lung disease. Flu vaccines are as immunogenic in pregnant women as in other adults, and no unusual complications have been encountered in pregnant women. The vaccines are killed virus preparations and, thus, safe for use during pregnancy. Prevention of influenza in pregnant women can be achieved with vaccination. See Chapter 25 for detailed discussion of influenza vaccine. The Advisory Committee on Immunization Practices (ACIP) recommends that all pregnant women who will be in second or third trimester during flu season receive influenza vaccine (4).

Enteroviruses

The enteroviruses consist of three major groups: the polioviruses, coxsackieviruses, and echoviruses. These viruses are a subgroup of the picornaviruses. Enteroviruses are small viruses (18 to 30 nm) with an RNA core. They occur worldwide, both in sporadic and epidemic form, and cause various illnesses (2,3,4,5 and 6). Congenital and neonatal infections have been associated with polioviruses, echoviruses, and coxsackieviruses (1,2,3,4,5,6,7 and 8). Cherry (2) noted that enterovirus infections of the fetus and newborn are more severe than similar infections in older age-groups. He felt that the relatively immature neonatal immune system might explain this phenomenon.

Polioviruses

Since the introduction of polio vaccines, poliomyelitis is an uncommon disease in Western industrialized nations. Only a brief review of the effects of polioviruses on pregnancy and the neonate is presented. Investigations in the prevaccine era clearly demonstrated that poliovirus infections during pregnancy could result in spontaneous abortion, stillbirth, low-birthweight infants, and neonatal poliomyelitis (1,9,10 and 11). Although poliovirus can be transmitted across the placenta to the fetus, most pregnant women (nearly two thirds) with clinically apparent poliomyelitis delivered healthy full-term babies (1). There is no evidence that polioviruses are teratogens, and no increase in congenital malformations has been noted (9,10 and 11).

Echoviruses

A total of 33 echoviruses have been identified (several have been reassigned to other groups of viruses). The echoviruses are responsible for various illnesses in adults and children, including respiratory disease, rashes, gastroenteritis, conjunctivitis, aseptic meningitis, and pericarditis (12).

Echovirus infection in pregnancy has not been associated with spontaneous abortions, premature delivery, stillbirths, or congenital malformations (1,2,12,13,14 and 15). There have been reports of neonatally acquired infections caused by many of the echoviruses. The clinical findings associated with neonatal echovirus infection include fever with splenomegaly and lymphadenopathy, macular rashes, diarrhea and vomiting, pneumonitis, otitis media, jaundice, coryza with cough, and septic meningitis (1,2,12). However, congenital echovirus infection can produce severe disease and damage to the neonate. Echovirus 14 was reported to be the cause of a febrile illness that developed at 3 days of life and progressed to cyanotic episodes, hypothermia, hepatomegaly, bradycardia, and purpura, with resultant death at 7 days of life (15). Echovirus 19 was reported to have caused hepatic necrosis and massive hemorrhage in three infants (17). No specific treatment or vaccines are available for echovirus infections.

Coxsackieviruses

The coxsackieviruses are divided into two major groups. Group A coxsackievirus contains 23 types, and group B includes 6 types. Group A coxsackieviruses do not

cause significant perinatal illness, except in rare cases.

Group B coxsackieviruses can cause pleurodynia, meningoencephalitis, and myocarditis. Hepatitis, the hemolytic uremic syndrome, and pneumonia are infrequent but severe manifestations of group B coxsackievirus infection. Transplacental transmission of group B coxsackievirus has been demonstrated (18,19,20 and 21). However, the magnitude of the risk to the fetus has not been defined. Most maternal group B coxsackievirus infections result in no demonstrable adverse effects on the fetus. No evidence demonstrates a role for coxsackieviruses in spontaneous abortion (15) or preterm labor and delivery.

In a study involving nearly 23,000 pregnancies, Brown and Karunas (13) reported that coxsackieviruses B2, B3, B4, and A9 had a positive correlation between maternal infection and neonatal anomalies (13). Coxsackievirus B4 infection in the first trimester has been associated with urogenital malformations, such as hypospadias, epispadias, and cryptorchidism. Coxsackievirus A9 maternal infection was associated with digestive tract anomalies, and types B3 and B4 were associated with cardiovascular defects. There was an association between the B1 through B5 coxsackievirus group and congenital heart disease. In addition, Brown and Karunas (13) found no correlation between reported maternal illness and serologic evidence of infection in the offspring. Thus, even asymptomatic maternal coxsackievirus infection may result in fetal maldevelopment.

Congenital coxsackievirus infection within 48 hours of birth is a rare occurrence (1). Neonatal infection with coxsackievirus can be acquired from mother, nursing personnel, or infected babies in the nursery. Many studies have documented the variety and severity of neonatal coxsackievirus infection, particularly types B1 through B5. Most have focused on myocarditis and CNS infection (1,2). Myocarditis seems to be a particularly prominent manifestation of group B coxsackievirus infection in the neonate.

Diagnosis of coxsackievirus infection is based on virus isolation from throat or rectum and serologic evidence of increasing antibody titer during the convalescent period. HI or CF tests may be performed.

Condylomata Acuminata And Human Papillomavirus Infection

The condylomata acuminata anogenital warts are caused by infection due to human papillomavirus (HPV) (1). Today, they are of great interest because of a dramatic increase in frequency and their implication in genital tract malignancy and juvenile and respiratory papillomatosis. HPV has not yet been cultured but is known to be a DNA virus. There are more than 60 types of HPV, which have been classified by risk of neoplasia. Low-risk types are 6, 11, 42, 43, 44, 53, 54, and 55; high-risk types are 16, 18, 45, and 56; and intermediate-risk types are 30, 31, 33, 35, 39, 51, 52, 58, and 66 (2).

Epidemiology

From 1970 to 1985, there was a fourfold increase in this infection. The prevalence of HPV in the genital tract varies widely, depending on the detection technique used and the population tested. In patients with normal cervical cytology and examination,

the rate is as low as 6%, but in women with cervical neoplasia, it is detected in more than 60% (2). It is widely believed that condylomata may proliferate and become friable in pregnancy (3), perhaps because of the “immunosuppressive” state of pregnancy. Lesions may cause soft tissue dystocia, extreme discomfort, difficulty in urinating or defecating, and hemorrhage with vaginal delivery (4).

HPV infections, most likely, are spread by direct skin-to-skin contact. The major mode of spread is sexual activity. However, HPV DNA has been detected on underwear and surgical instruments, as well as on swabs in 20% of virginal college-age women when sensitive polymerase chain reaction (PCR) techniques were used (2). Thus, other modes of transmission—other than sexual—are possible. It is estimated that contagion is relatively high. Condylomata acuminata have been reported on an infant at birth. Respiratory papillomatosis results in warts of the larynx and trachea. In about 60% of juveniles with this condition, genital condylomata were present in the mother at delivery.

HPV infection has a relatively long, though variable, incubation period, with a range of 3 to 8 months. As with other sexually transmitted diseases (STDs), warts may occur in concert with gonorrhea or other STDs. Most cases occur between ages 16 and 25.

Diagnosis

The classic wart is a soft excrescence, several millimeters in diameter, often taller than it is wide. They may occur singularly or in clusters. Occasionally, there are “giant” condylomata up to 3 cm or more in diameter. These are soft and round, with a pebbled surface. Warts are commonly located in moist areas and are often found in the vaginal introitus, vagina, and vestibule. Minute flat warts, often visible only with the colposcope, are common on the cervix.

Often, the diagnosis is made clinically. Condylomata lata should be ruled out, by use of a syphilis serologic test. In suspect or atypical lesions, biopsy may be necessary to rule out malignancy.

Juvenile Respiratory Papillomatosis

Respiratory papillomatosis may be of either juvenile or adult onset. About one third to one half of cases are evident by age 5. With the vocal cords, the most common site, hoarseness is the most frequent symptom. Occasionally, papillomas may produce respiratory obstruction.

Because of the historic similarity between respiratory papillomas and genital warts, an HPV etiology had been suspected in the former. Recent studies have established that warts of these two locations are virologically indistinguishable, with 90% from both locations being HPV-6 or HPV-11 (5).

Perinatal transmission has been the subject of recent study. In approximately 60% of mothers with infants afflicted with respiratory papillomatosis, there is detection of HPV DNA (2). Although it has been estimated that 2% to 5% of all births in the United States are at risk for perinatal HPV exposure, juvenile respiratory papillomatosis remains are (approximately 1,550 cases per year; a rate of 0.04% of

all vaginal deliveries) (2). It is speculated that its perinatal transmission may occur by ascension into the uterus or by direct contact during birth.

To estimate the rate of transmission during vaginal delivery, Shah et al. (5) examined the frequency of cesarean delivery in 109 cases of respiratory papillomas (onset before the age of 14). It was presumed that cesarean delivery, before rupture of membranes, would prevent intrapartum transmission but not prevent other modes. Because of the rarity of the condition, cases were collected from three sources. All cases were biopsy proven. Only 1 (1%) of the 109 cases had a history of cesarean delivery. On the basis of national cesarean section rates in relevant years, the authors estimated that there would have been ten cesarean births in these 109 patients. The child developing respiratory papillomatosis after cesarean delivery was born by section before membrane rupture. The authors concluded that in juvenile-onset respiratory papillomatosis, mother-to-infant transmission occurs most often during vaginal delivery but that *in utero* infection is also possible. Further, in view of the frequency of genital warts and the rarity of juvenile-onset respiratory papillomatosis, the authors estimated the risk of developing disease for a child born to an infected mother. On the basis of crude annual rates of births and new cases of respiratory papillomatosis, the estimate was one in several hundred (range, 1 : 80 to 1 : 1,500).

Perinatal transmission of HPV DNA has been evaluated in several recent works. Using a PCR assay, Puranen et al. (6) assessed 106 infants born by vaginal delivery or by cesarean section and their 105 mothers. Both mothers' and infants' samples were positive for the same type of HPV in 29 mother-infant pairs. It was noted that five infants born by cesarean delivery were found to have the same type as the mother. Overall concurrence between HPV types and her newborn was 69% (29 of 42). HPV DNA was found in 39 (37%) of 106 infants. It should be noted that infant specimens were taken immediately after birth from a nasopharyngeal aspirate (6). In a study of similar design in the Republic of China, specimens from the neonate were collected by swab from the buccal mucosa and from the genitalia, on day 3 or 4 of life. The investigators found that the overall frequency of HPV transmission from HPV-16–positive or HPV-18–positive mothers was 39% (27 of 68). A significantly higher rate of transmission was found when infants were delivered vaginally than by cesarean delivery (51.4% vs. 27.3%; $p = 0.042$) (7). Both of these studies assessed newborns very early in the newborn period. On the other hand, Watts et al. (8) found much lower transmission rates when infants were followed for longer intervals. During pregnancy, 112 (74%) of 151 women had evidence, by history, clinical, or DNA testing, of genital HPV infection. At nearly 500 infant visits, HPV DNA was detected with low prevalence, from only 5 of 335 genital specimens (1.5%), from 4 of 324 anal specimens (1.2%), and from none of 372 oral or nasopharyngeal specimens. The rate of isolation did not vary over the interval of follow-up from 6 weeks to 36 months. Although the authors were not able to rule out perinatal transmission, they observed that the upper 95% CI for detection of perinatal transmission from women with evidence of human genital HPV infection was only 2.8% (8).

Based on the use of cesarean section to prevent neonatal herpes when the mother is infected with herpes at labor, delivering babies of mothers with genital warts by cesarean section might be suggested. However, authors including the American College of Obstetricians and Gynecologists and CDC do not support that position, and we know of no current data to recommend that strategy (2,3). First, the risk of

transmission of the disease is low (probably ten times lower than with herpes). Second, cesarean delivery does not offer complete protection, and we do not know exactly what protection is offered. Third, it is likely that the risks of cesarean section for all women with any genital warts would outweigh the potential benefits (2,5).

Treatment Of Condylomata Acuminata In Pregnancy

General predisposing features, such as other vaginitis, should be corrected, and the genital area should be kept clean with avoidance of excess moisture.

In addition to the concern for transmission of HPV to the neonate, warts in pregnancy may lead to tearing or bleeding during delivery, particularly when they are large or extensive. Thus, genital warts in pregnancy should be treated when recognized in pregnancy. Many have noted that condylomata acuminata may thrive in pregnancy, perhaps due to a relative maternal immunosuppression.

Specific treatment considerations of genital warts should be modified in pregnancy. Podophyllum is best avoided in pregnancy, as it may be absorbed and can be toxic to the fetus. Large doses of podophyllum (7.5 mL of 25% solution, containing 1.88 g of podophyllum) used to treat florid vulvar warts were associated with fetal death 2 days later (9). Maternal neurologic and respiratory symptoms were also reported in this overdose. In animals, podophyllum is both teratogenic and neurotoxic (9). Congenital anomalies were reported in the infant of a woman who ingested podophyllum tablets.

A purified preparation, 0.5% podofilox, is available for treatment of external warts, but this preparation should not be used on the vagina or cervix or in pregnancy (2).

Topical 5-fluorouracil (5-FU) is contraindicated in pregnancy (2). Several years ago, there were individual case reports of multiple congenital anomalies associated with use in the first trimester and of “neonatal intoxication” from 5-FU used at midpregnancy. More recently, there have been case reports of periconceptional 5-FU exposure without adverse effects, but these few cases do not exclude a high potential risk (10,11).

Interferons have been used to treat persistent condylomata, but with varying effectiveness. There has been little use of these agents in pregnancy, and they are considered contraindicated in pregnancy (2).

Topical trichloracetic acid (85%) or bichloracetic acid may be used in pregnancy. They work best on moist mucosal warts. Cure rates from a single application are limited (estimated at 20% to 30%, except for very small lesions), thus necessitating re-treatment every 7 to 10 days (4). Trichloracetic acid has also been combined with laser treatment for condylomata in pregnancy (4).

Condylomata in pregnancy may also be treated with cryosurgery when they occur in the vagina or on the vulva. In 1987, Berman et al. (12) reported a series of 28 pregnant women treated with cervical cryotherapy. They reported favorable responses with no adverse effects on the pregnancies (12). For isolated large condylomata, surgical excision would be appropriate in a pregnant woman. Treatment may be carried out with electrocoagulation with curettage (13). A recent

addition to the armamentarium for treating HPV is imiquimod (Aldara Cream), an immune response modifier. It is available as a 5% cream with applications to be made by the patient three times per week for up to 16 weeks until the warts are gone. The exact mechanism of action is unknown, although it does not have direct antiviral activity in cell culture. It is presumed that imiquimod induces cytokines such as interferon alpha, interleukins, and tumor necrosis factor. After application of imiquimod cream, there is minimal systemic absorption, and the cream is generally well tolerated. Less than 2% of patients discontinued therapy because of adverse effects, but the most common application site reactions were itching (32%), burning (26%), pain (8%), and soreness (1%). Imiquimod 5% cream is rated as pregnancy category B by the FDA; however, there are no adequate controlled studies of use of this preparation in pregnancy (14).

Human Parvovirus

The human parvoviruses are a family of DNA viruses, of which human parvovirus B19 is the only known human pathogen (1,2). Parvovirus B19 is a small (12-nm) single-stranded DNA virus. Human parvovirus was discovered in 1975 and in 1981 was shown to be an etiologic agent of transient aplastic anemia (3,4). The virus was identified as the etiologic agent of erythema infectiosum (fifth disease), a common childhood viral exanthem in 1983 (5,6). The virus has a predilection for the hematopoietic system and is cytotoxic for erythroid progenitor cells. The most common manifestation of human parvovirus B19 is erythema infectiosum (fifth disease). Parvovirus has also been implicated in aplastic crises in patients with chronic hemolytic anemia. In 1984, after epidemics of erythema infectiosum, parvovirus B19 was shown to cause *in utero* infection and nonimmune hydrops of the fetus (7,8).

Human parvovirus B19 is worldwide in distribution and is most common in young children, ages 5 to 14 years. Parvovirus B19 is a very common infection in which seroprevalence of antibody to parvovirus B19 IgG is age dependent. As reviewed by Anderson (1), the reported prevalence ranges, by age, are as follows: (a) 1 to 5 years, 2% to 15%; (b) 5 to 19 years, 15% to 60%; and (c) adults, 30% to 60%. It is estimated that 50% to 75% of reproductive-age women are immune to parvovirus B19, based on serologic evidence of previous infection. Clinical disease may be epidemic or sporadic. The most common manifestation in children is erythema infectiosum, which has a winter and spring seasonality. In children, disease tends to be clinically mild and presents with a low-grade prodromal fever that precedes to the development of a very characteristic rash; the rash is an erythematous, warm “slapped cheek”–like facial rash. This is followed by a morbilliform rash of the extremities. In adults, the disease usually is asymptomatic. However, in clinical cases, it presents with fever, adenopathy, arthralgias, and mild arthritis, particularly of the hands, wrists, and knees. This polyarthropathy occurs in 50–80% of infected adult women (9). Rash is usually not present in adults.

In the United States, 50% to 75% of women in the reproductive age-group are immune and demonstrate antibodies against human parvovirus B19. The organism is a highly infectious agent and 60% to 80% of susceptible household contacts will become infected when exposed to childhood disease. Among seronegative schoolteachers and day care workers who are at risk during epidemics, 20% to 30% will develop the disease (10).

Among susceptible teachers, two factors were shown to be associated with an increased risk of parvovirus B19 infection (10): (a) teachers of young children and (b) exposure in the classroom to many children with rash. Bell et al. (11) reported that 36% and 38% of susceptible health care workers became infected after exposure to children with aplastic anemia. Recently, Adler et al. (12) identified risk factors for parvovirus B19 infection for hospital and school employees during nonepidemic periods. In the absence of an epidemic of parvovirus B19 infection, the annual seroconversion rate for hospital workers was 0.42% and that for school employees was 2.93%. This compares with secondary attack rates of 20% to 40% during epidemic periods. Their data demonstrated that contact with elementary school-aged children at home or at work was the most important risk factor for parvovirus B19 acquisition (12). Individuals had approximately a twofold greater risk of acquiring parvovirus B19 from children at work than at home (12). However, they showed a low seroconversion rate among hospital employees without known contact with children. This is in contrast to exposure of hospital workers to patients with aplastic anemia (11). Thus, Adler et al. (12) recommended that pregnant women with unknown or susceptible serologic status should not care for patients with hemolytic anemia and fever or aplastic crisis. Recently, Valeur-Jensen et al. screened nearly 31,000 pregnant women in Denmark and noted that 65% had evidence of past Parvovirus B19 infection (13). Annual seroconversion rates among susceptible women during endemic and epidemic periods were 1.5% (95% CI 0.2–1.9) and 13% (95%) CI 8.7–23.1) respectively (13). Baseline seropositivity was significantly associated with increasing number of siblings, having a sibling of the same age, number of own children, and occupational parvovirus infection increased in parallel with the number of children in the household. Compared with other pregnant women, nursery school teachers had a 3-fold increased risk of acute infection (OR 3.09%; 95% CI 1.62–5.89) (13). These authors etimated that the population-attributable risk of seroconversion was 55.4% for number of own children and 6% for occupational exposure (13). Thus, the risk of infection is high for susceptible pregnant women during epidemics and is associated with the level of contact with children (13). Nursery school teachers had the highest occupational risk, but most infections appear to result from exposure to the woman's own children (13).

The diagnosis is generally made on clinical grounds, particularly in children. Antibody tests for parvovirus B19 have become available. An ELISA method is currently recommended for IgG- and IgM-specific antibodies to human parvovirus B19 (9). Acute parvovirus infection can be documented by a combination of clinical symptoms and signs of parvovirus B19 infection and the presence of parvovirus B19 IgM antibodies, the virus (e.g., by culture, PCR, *in situ* hybridization), or typical histologic changes in red blood cell precursors (14,17). Parvovirus B19 IgM antibody appears within a few days of onset of illness (13). The gold standard test for detection of anti-B19 IgM antibody is the IgM antibody capture radioimmunoassay (MACRIA) (18). The most sensitive tests for detection of virus include PCR for parvovirus B19 DNA and nucleic acid hybridization for parvovirus B19 DNA (13).

The fetus has also been shown to be at risk for parvovirus B19 infection. The risk to the fetus has received tremendous attention over the last decade since initial reports in the late 1980s suggested that during pregnancy, human parvovirus B19 may result in fetal hydrops and stillbirth (19,20,21 and 22). The pathogenesis of this disease revolves around the predilection of human parvovirus B19 for human erythroid progenitor cells. With intrauterine transmission to the fetus, the fetus is at risk for

developing aplastic anemia secondary to this predilection. The rapidly expanding red blood cell volume, a shorter half-life of red blood cells in the fetus, and an immature immune system make the fetus particularly susceptible to the effects of parvovirus B19. In general, fetal hydrops occurs 4 to 6 weeks after maternal infection, with a range of 1 to 12 weeks. Parvovirus B19 causes erythroid hypoplasia, shortened red blood cell survival, and hemolysis. The resultant anemia leads to high-output cardiac failure, which results in fetal hydrops.

Although early reports suggested a high rate of transmission to the fetus (38%) and a significant morbidity to the fetus and mortality with human parvovirus infection, more recent work has demonstrated that maternal infection produces no adverse effects on the fetus in most cases. Early small cases studies suggest a high rate of transmission to the fetus. Woernle et al. (20) reported that 4 of 12 pregnant women at risk for parvovirus B19 were IgM positive. In this group, one of the four fetuses was a stillbirth due to hydrops. Previous reports had described 22 pregnant women with serologic evidence of parvovirus B19 infection, in whom nine fetal deaths occurred. In 1988, Rodis et al. (21) reviewed 37 reported cases of women exposed and infected during pregnancy. In this retrospective study, they reported that 14 of the pregnancies (38%) had adverse outcomes, including spontaneous abortions, intrauterine fetal death, and congenital anomalies. Eleven of the 37 fetuses had intrauterine nonimmune fetal hydrops. Similarly, in another retrospective study, Schwartz et al. (23) reported that 10 (26%) of 39 susceptible pregnancies developed fetal hydrops; 7 of these infants died *in utero,* and 3 who had received intrauterine transfusions survived.

More recent prospective studies have cast doubt on this high rate of fetal transmission. In England, the Public Health Laboratory Service Working Party on Fifth Disease reported a fetal death rate of 16% in a large series of 190 pregnancies; however, only 6 of the 14 fetuses tested were DNA positive for human parvovirus B19 (24). These authors reported a fetal loss rate of 14% (1 of 14) after 20 weeks of gestation and a 17% loss before 20 weeks, which is similar to that in the general population (24). Moreover, if the documented rate of parvovirus B19 infection (6 of 14) is applied to all 30 fetal deaths, an upper limit estimate for parvovirus B19–related fetal death among infected women would be 9.7% (24). In a prospective study undertaken during a 1988 epidemic of erythema infectiosum in Connecticut, Rodis et al. (25) reported that among 39 pregnant women with evidence of recent infection during pregnancy, 37 (95%) delivered healthy newborns and only 2 (5%) had spontaneous abortions, of which only 1 was related to human parvovirus B19. No infants developed fetal hydrops in this series. Similarly, in the United States in a large prospective study that screened 3,526 pregnant women, the CDC (21) concluded that although the risk for fetal death was increased, particularly in the first 20 weeks of gestation, this did not reach statistical significance (Table 16.15). There was a 5.9% fetal death rate among infected women, compared with 3.4% among controls (26). The CDC noted no increase in preterm delivery; birthweights were similar in those infected with parvovirus B19 and in controls; and no increase in birth defects occurred among the infants infected with parvovirus B19. Table 16.15 summarizes the findings of prospective studies assessing the effect of maternal parvovirus B19 infection on pregnancy outcome. Overall the risk for fetal death was 7% and the risk for non-immune hydrops 1% (24,25,26,27,28,29 and 30).

Study	No. of Cases	Fetal Death	Hydrops Fetalis
Public Health Laboratory Service (24)	186	17	1
Centers for Disease Control (26)	49	2	1
Rodis et al. (25)	35	2	0
Guidozzi et al. (27)	63	1	0
Grataco et al. (28)	60	1	0
Harger et al. (29)	52	0	0
Miller et al. (30)	477	43	7
Total	926	66 (7%)	9 (1%)

TABLE 16.15. PREGNANCY OUTCOMES AMONG WOMEN SCREENED FOR HUMAN PARVOVIRUS B19 INFECTION

Women exposed to erythema infectiosum during pregnancy should be screened serologically for IgG and IgM antibodies against parvovirus. If IgG antibody is present, this denotes immunity against the disease, and these patients can be reassured. Those who are IgG negative and IgM negative are susceptible to infection and should be cautioned to reduce their risk of exposure, particularly if they are schoolteachers or work in day care centers during epidemics of fifth disease. The women who are IgG negative and IgM positive and in whom acute parvovirus infection is thus confirmed should be closely evaluated and monitored for the development of intrauterine fetal hydrops (Fig. 16.6). For women with a documented infection, maternal serum a fetoprotein (AFP) determinations (31,32) and diagnostic ultrasound examinations are used to detect the development of hydrops. In general, maternal serum AFP level will be elevated before the onset of hydrops, as demonstrated by sonography. Serial maternal serum AFP determinations are obtained. If the maternal serum AFP level becomes elevated, serial ultrasound examinations are obtained. More commonly, only serial ultrasound screening for detection of hydrops is utilized. Ultrasounds should be repeated weekly for up to 12 weeks. Hydrops usually occurs 4 to 6 weeks postinfection.

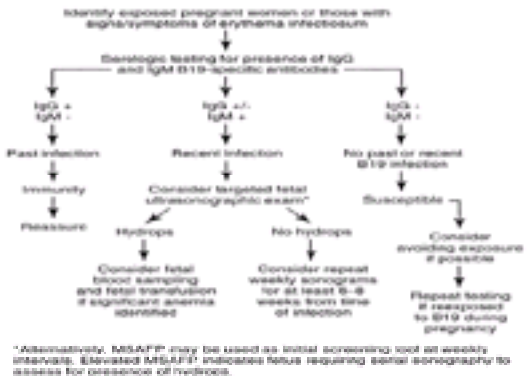


FIGURE 16.6. Suggested protocol for management of pregnant women exposed to parvovirus B19.

Once intrauterine evidence for hydrops develops, two alternatives are available. Until recently, intrauterine blood transfusion, usually via percutaneous umbilical blood sampling, has been proposed for the treatment of the hydropic fetus with parvovirus B19–induced anemia and has been very successful (23,32,33,34,35 and 36). However, several recent studies have noted the occurrence of fetal hydrops in association with acute parvovirus infection that resolved spontaneously over 4 to 6 weeks without intrauterine transfusion (37,38). Thus, the role of intrauterine blood transfusion in preventing intrauterine stillbirth due to hydrops secondary to aplastic anemia remains unclear. Possibly, the younger fetus, with less than 20 to 22 weeks of gestation, is at risk and requires intrauterine transfusion, whereas the older fetus, in the latter part of the second trimester, with a more functional immune system, may be better able to tolerate the insult from the parvovirus infection.

Fairley et al. (39) demonstrated the benefit of intrauterine transfusion in a series of 66 cases of fetal hydrops in England and Wales. Among the 38 fetuses alive at the time of initial ultrasound, 3 of 12 transfused and 13 of 26 not transfused died in utero. After adjustment for severity of hydrops (ultrasound) and gestational age, the risk of death among those transfused was significantly reduced (O.R. 0.14; 95% C.I. 0.02–0.96) (39).

No vaccine or treatment is available for human parvovirus infection. Thus, prevention by avoiding exposure to erythema infectiosum is the only method available. As discussed in previous sections, parvovirus B19 is highly contagious. High-risk groups for exposure and acquisition of infection are day care workers, elementary schoolteachers, hospital employees caring for patients with aplastic anemia, and household members with an infected child. As reviewed by Adler (12), secondary attack rates for high-risk susceptible women are 20% to 40% during epidemic periods and 2% to 5% during endemic periods. Although these are worrisome rates, available data now show that the risk to the fetus after maternal infection is low (12,19,20 and 21). Adler (12) calculated (assuming that on average 50% of pregnant women are susceptible, during an endemic period 1% to 4% of susceptible women acquire infection, and the rate of fetal death after maternal infection is 5% to 10%) that the occupational risk of fetal death due to parvovirus B19 infection for a pregnant woman with unknown serologic status is between 1 of 500 and 1 of 4,000. Thus, during endemic periods, these rates are so low that intervention such as serologic screening of pregnant women or furloughing or temporarily transferring pregnant seronegative employees to non–child care areas is not justified (12). On the other hand, during epidemic periods, when infection rates may be 5- to 20-fold higher, serologic testing or temporary transfer of pregnant employees may be appropriate (12).

However, for most women, the source of fetal parvovirus B19 infection is exposure to school-aged children at home. No good method of prevention is applicable to this situation. Thus, to a large extent, prevention of maternal parvovirus must await development of an effective vaccine that can be administered to infants.

BACTERIA

Syphilis

The epidemiology, clinical presentation, diagnosis, and treatment of syphilis is discussed in detail in Chapter 7 (Sexually Transmitted Diseases).

Treatment

Penicillin is the drug of choice for the treatment of syphilis in nonpregnant patients and pregnant women. The recommended treatment schedule suggested by the CDC is presented in Table 16.16.

Early syphilis (primary, secondary, and latent syphilis <1-yr's duration)
Penicillin G benzathine, 2.4 million U i.m. as a single dose
Syphilis of >1-yr's duration
Penicillin G benzathine, 2.4 million U i.m. weekly for three doses (total, 7.2 million U)
Neurosyphilis
Aqueous crystalline penicillin G, 2-4 million U i.v. every 4 hr for 10-14 d followed by penicillin G benzathine, 2.4 million U i.m.
or
Aqueous penicillin G procaine, 2.4 million U i.m. daily, plus probenecid 500 mg p.o. q.i.d., both for 10-14 d, followed by penicillin G benzathine, 2.4 million U i.m.

i.m., intramuscularly; i.v., intravenously; q.i.d., 4 times a day.

TABLE 16.16. CENTERS FOR DISEASE CONTROL AND PREVENTION–RECOMMENDED TREATMENT OF SYPHILIS IN PREGNANCY (2001)

Current CDC recommendations suggest that patients with a history of allergy to penicillin should be tested to confirm the allergy and then desensitized to penicillin and treated with penicillin in the dosage schedule appropriate for the duration of syphilis (Chapter 7, Sexually Transmitted Diseases).

Listeriosis

Listeriosis is an infection caused by *Listeria monocytogenes,* a facultative, motile non–spore-forming Gram-positive rod. Although seven species of *Listeria* have been identified, *L. monocytogenes* is the principal pathogen in humans (1). *L. monocytogenes* is indistinguishable from diphtheroids on morphologic grounds and thus is often discarded as a contaminant by clinical laboratories (1). Sixteen serotypes (serovars) of *L. monocytogenes* have been identified, of which three (i.e., 46, 1/2b, 1/2a) are responsible for more than 90% of clinical infections (1). Although the organism is easily isolated from normally sterile sites (e.g., placenta, amniotic fluid, and blood) on routine culture media, it can be difficult to recover from mixed cultures such as vaginal or cervical specimens (1). Use of selective media and enrichment techniques will improve the yield from such sites. Listeriosis causes an estimated 2500 serious illnesses and 500 deaths annually in the United States.

Patients who are immunocompromised and pregnant women and their newborns are particularly susceptible to infection with *L. monocytogenes.* Of concern to the obstetrician is the association between maternal listerial infection and preterm labor and fetal infection. High perinatal morbidity and mortality rates have been reported for listerial infection in pregnancy (2,3,4,5 and 6).

As with group B streptococcal infection, neonatal listeriosis has been divided into two serologically and clinically distinct areas. Serotypes Ia and IVb have been associated with early-onset listeriosis. Early-onset disease takes the form of a diffuse sepsis with multiorgan involvement including pulmonary, hepatic, and the CNS. Early-onset listeriosis is associated with high stillbirth and neonatal mortality rates. Early-onset listerial infection appears to occur more frequently in low-birthweight infants.

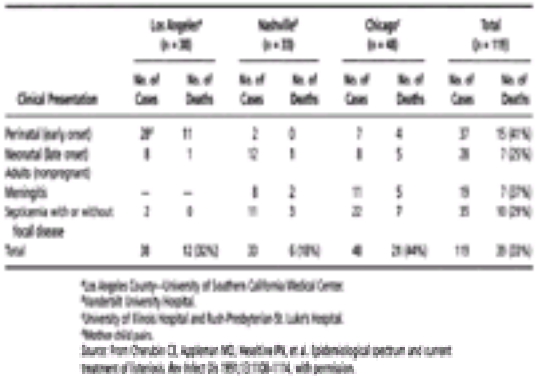
Like group B streptococcus infection, late-onset listeriosis presents as meningitis. These infants are usually full-term and born to mothers with uneventful perinatal courses. Neurologic sequelae such as hydrocephalus or mental retardation are common with late-onset disease. In addition, a mortality rate approaching 40% is reported.

Although Charles (2) suggested that an ascending route of infection from cervical colonization with *L. monocytogenes* (even across intact membranes) plays a role in the pathogenesis of neonatal infection, the more important and common route of infection is secondary to maternal infection, leading to placental infection that then leads to fetal septicemia and multiorgan involvement in the fetus. It is felt that amniotic fluid becomes infected with *Listeria* secondary to excretion of the organism via fetal urination. Aspiration and swallowing of infected amniotic fluid may then result in respiratory tract involvement of the infection in the fetus.

Human listeriosis presents in both epidemic and sporadic forms. The epidemic orm has clearly been associated with contamination of food and food products. Since 1981, four major outbreaks of listeriosis (three in North America and one in Switzerland) have occurred, which clearly document food-borne transmission in epidemic listeriosis (7,8,9 and 10). The first was a 1981 outbreak of listeriosis in Nova Scotia (7). In this outbreak, 34 perinatal cases and 7 adult cases were identified. The case fatality rate for infants born alive was 27%, and there were 19 intrauterine deaths (7). In the Massachusetts outbreak of 1983, the epidemiology was different, with most cases (42 of 49) occurring in immunocompromised adults and only seven cases of perinatal listeriosis were reported (8). In both adult and neonatal cases, the case fatality rate was 29% (8). In Los Angeles, from January 1, 1985, through August 15, 1985, 142 cases of human listeriosis were reported in association with ingestion of cheese contaminated by *L. monocytogenes.* Two thirds of these infections occurred in pregnant women or their offspring, and 30 of the 48 deaths in this epidemic occurred in fetuses or neonates (9). The case fatality rate for the 49 nonpregnant adults was 33% (9). In 1988, an epidemic of listeriosis was reported in Switzerland, involving 122 cases (64 perinatal and 58 nonpregnant adults); the case fatality rate was 28% (10).

In a recent report from Finland of 74 cases of systemic listeriosis from 1971 to 1989, a mortality rate of 30% was noted among the neonates infected with *L. monocytogenes* (11). Among the six pregnant women with listerial infection, five had fetal complications: three spontaneous abortions and two preterm deliveries. In the presence of underlying disease, the mortality rate in adults was 32% (11). All healthy

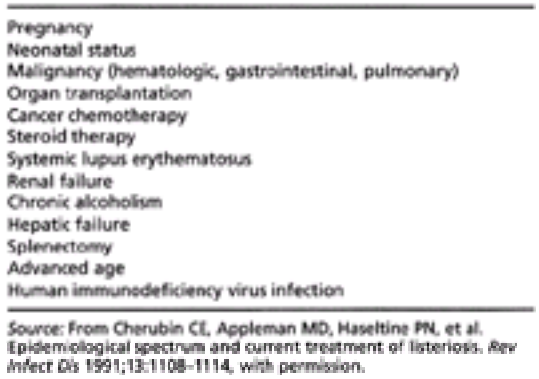
nonimmunocompromised nonneonatal patients survived the listerial infection. Cherubin et al. (12) reviewed more than 120 cases of listeriosis from four medical centers in three geographically separated sites (Los Angeles, Nashville, and Chicago). Although in Los Angeles, more than two thirds of cases occurred during the perinatal period, at Vanderbilt University Hospital in Nashville, most cases occurred in older adults who had received organ transplants (Table 16.17) (12). In Chicago, an intermediate pattern with a more equal mix of perinatal and adult cases of meningitis, bacteremic, or neurologic infections was seen (12). These authors identified risk factors for listeriosis (Table 16.18). Among the most important are pregnancy, neonatal status, organ transplantation, malignancy, renal failure, systemic lupus erythematosus, steroid therapy, and HIV infection (12). These authors stressed that mortality associated with listeriosis occurred predominantly among premature infants and stillbirths delivered by infected pregnant women (12). The earlier the stage of gestation when infection occurred, the higher the risk for fetal death, with a mean gestational age of 25.9 weeks for fetuses or neonates who died, compared with 33.7 weeks for surviving infected infants (12). Mortality rates were markedly decreased among neonates (particularly term) and adults (12). These studies demonstrate that *Listeria* is prone to adversely affect immunocompromised adults and fetuses or neonates with immature immune systems.



Clinical Presentation	Los Angeles[a] (n = 38)		Nashville[b] (n = 33)		Chicago[c] (n = 48)		Total (n = 119)	
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths
Perinatal (early onset)	28[d]	11	2	0	7	4	37	15 (41%)
Neonatal (late onset)	8	1	12	1	8	5	28	7 (25%)
Adults (nonpregnant)								
Meningitis	—	—	8	2	11	5	19	7 (37%)
Septicemia with or without focal disease	2	0	11	3	22	7	35	10 (29%)
Total	38	12 (32%)	33	6 (18%)	48	21 (44%)	119	39 (33%)

[a] Los Angeles County–University of Southern California Medical Center.
[b] Vanderbilt University Hospital.
[c] University of Illinois Hospital and Rush-Presbyterian St. Luke's Hospital.
[d] Mother-child pairs.
Source: From Cherubin CE, Appleman MD, Haseltine PN, et al. Epidemiological spectrum and current treatment of listeriosis. *Rev Infect Dis* 1991;13:1108–1114, with permission.

TABLE 16.17. SUMMARY OF CASES AND MORTALITY FOR LISTERIOSIS BY GEOGRAPHIC SITE IN THE UNITED STATES



Pregnancy
Neonatal status
Malignancy (hematologic, gastrointestinal, pulmonary)
Organ transplantation
Cancer chemotherapy
Steroid therapy
Systemic lupus erythematosus
Renal failure
Chronic alcoholism
Hepatic failure
Splenectomy
Advanced age
Human immunodeficiency virus infection

Source: From Cherubin CE, Appleman MD, Haseltine PN, et al. Epidemiological spectrum and current treatment of listeriosis. *Rev Infect Dis* 1991;13:1108–1114, with permission.

TABLE 16.18. RISK FACTORS FOR LISTERIOSIS

More commonly, listeriosis occurs sporadically (sporadic or endemic listeria) (1). Two studies by the CDC have established a baseline incidence for sporadic listeriosis in the United States (13,14). Using hospital discharge data from the Commission on Professional and Hospital Activity, Ciesielski et al. (13) reported that from 1980 to 1982, there were an estimated 800 cases of listeriosis annually, for an incidence of 3.6 cases per 1 million population and a minimum of 150 deaths, for a case fatality rate of 19%. Attack rates were noted to be highest among newborns (4.7 per 100,000 livebirths per year) and those 70 years or older (11 per 1 million population). Using a population-based active-surveillance study, the CDC estimated that approximately 1,700 cases of listeriosis occurred in the United States in 1986 (14). This computes to an overall annual incidence rate of 7.1 cases per 1 million population. Among perinatal cases, the attack rate was 12.4 cases per 100,000 livebirths, and for nonpregnant adults, 5.4 cases per 1 million population (14). Among persons older than 70 years, the incidence was 21 cases per 1 million population (14). In nonperinatal cases, the overall fatality rate was 35%, ranging from 11% in persons younger than 40 years to 63% in persons older than 60 (14). In summary, listeriosis is estimated to cause at least 1,700 serious infections and contribute to approximately 450 deaths and 100 stillbirths annually in the United States (1).

It is unclear what role food-borne transmission plays in sporadic listeriosis. Schwartz et al. (15) hypothesized that such is the case. Individuals infected with *Listeria* from contaminated food may be asymptomatic and become chronic carriers of the organism in their gastrointestinal tract (16). Subsequently, such female organisms could colonize the vagina and cervix with *L. monocytogenes.*

Unfortunately, many pregnant women with listerial infection remain asymptomatic. When symptomatic, a flulike syndrome is characterized by fever, chills, headache, malaise, myalgia, back pain, and upper respiratory complaints. Associated gastrointestinal symptoms (e.g., diarrhea and abdominal cramping) are less common. These symptoms, or prodrome, occur in about two thirds of cases (17). This prodrome represents the bacteremic stage of listeriosis and is probably the time during which the uterine contents are seeded (1). Within 3 to 7 days, this prodrome can progress to amnionitis with resultant preterm labor and delivery, septic abortion, *in utero* fetal infection, stillbirth, or neonatal infection. Maternal infection tends to be mild and not associated with significant maternal morbidity. On occasion, diffuse sepsis may occur. Listeriosis occurs most frequently during the third trimester (1). Unfortunately, no specific clinical manifestations help distinguish listeriosis from other infections that may occur during pregnancy. Thus, pregnant women in the late second or early third trimester with the above-described prodrome need to be assessed for possible listeriosis.

Unlike maternal infection, neonatal listeriosis is commonly associated with morbidity and mortality, with fatality rates ranging from 3 to 50% in liveborn infants (14,17). As in group B streptococcus infection, two distant neonatal patterns of listerial infection

occur—early and late onset.

Early-onset neonatal listeriosis occurs in infants infected *in utero* before the onset of labor. Usually the mothers of these infants experienced the flulike prodrome (1). However, ascending infection from a colonized lower genital tract has also been documented (2,18). Early-onset infection manifests within the first few hours to few days of life. Widely disseminated granulomas are typical in severe newborn disease acquired *in utero.* The granulomas are found most commonly in the placenta and liver. Such granulomas may be clues to the diagnosis when neonatal sepsis presents within the first few days of life.

Late-onset neonatal infection due to *L. monocytogenes* usually occurs in full-term infants from uncomplicated pregnancies (1). Such infants appear healthy at birth and do not manifest their infection until several days to several weeks after delivery. With late-onset listerial infection, meningitis is more common than sepsis. It is assumed that postpartum acquisition is the route for late-onset infection with *L. monocytogenes.* Possibly, the organism is transmitted during passage of the fetus through the birth canal. Nosocomial transmission of *L. monocytogenes* has also been documented as a cause of late-onset neonatal listeriosis (1).

Because of the high mortality rate associated with both early- and late-onset neonatal listerial infection, it is crucial that the obstetrician maintain a high index of suspicion that any febrile illness in pregnancy may be due to *L. monocytogenes.* In such patients, cervical and blood cultures should be obtained for *L. monocytogenes* as soon as possible. Because colonies of *L. monocytogenes* may be mistaken on Gram stain for diphtheroids and thus ignored, it is important to inform the microbiologist that *Listeria* is a concern. In febrile pregnant women, a Gram stain revealing Gram-positive pleomorphic rods with rounded ends is very suggestive of *L. monocytogenes.*

Penicillin G and ampicillin are effective *in vivo* against *L. monocytogenes.* Current opinion holds that optimum therapy includes a combination of ampicillin and an aminoglycoside. Maternal treatment consists of ampicillin (1 to 2 g intravenously every 4 to 6 hours) and gentamicin (2 mg/kg intravenously every 8 hours). For the newborn, the ampicillin dosage is 200 to 300 mg/kg per day administered in four to six divided doses. Treatment is generally provided for 1 week. A recent report suggested that with documentation via amniocentesis of intrauterine listerial infection, antibiotic treatment without immediate delivery may be successful and result in a normal healthy fetus (19).

Guidelines for prevention of listeriosis are similar to those for preventing other food bourne illnesses (20). The general recommendations are: 1) cook thoroughly raw food from animal sources; 2) wash raw vegetables thoroughly before eating; 3) keep uncooked meats separate from vegetables and from cooked foods and ready-to-eat foods; 4) avoid raw (unpasteurized) milk or foods made from raw milk; and 5) wash hands, knives, and cutting boards after each handling of uncooked foods (20).

Tuberculosis

In just the last few years, there has been renewed interest in tuberculosis because of an increasing number of cases in women of reproductive age, reports of new cases

of congenital tuberculosis, and development of multidrug resistance. In June 2000, the CDC revised its recommendations for tuberculin testing and treatment of latent tuberculosis infection (1).

Epidemiology

Between 1985 and 1992, the number of cases in reproductive-age women increased 41% (2). In two hospitals in New York City, there was a dramatic increase among pregnant women—from 12.4 cases per 100,000 deliveries (five cases in 6 years) in 1985 to 1990 to 94.8 cases per 100,000 deliveries (11 cases in 2 years) in 1991 to 1992 (3). This increase parallels a national increase in tuberculosis cases (4). From 1985 through 1991, the number of reported tuberculosis cases increased 18%, largely due to the HIV epidemic, deterioration of the health care infrastructure, and increases of cases among foreign-born persons.

The recently reported case series from New York illustrates key points (3). Of the 16 patients in the study, only 5 had prenatal care before the diagnosis was made. The remaining 11 patients had their diagnoses confirmed when they sought care in the emergency department because of symptoms related to the infection. Ten of the 16 cases were proven active pulmonary tuberculosis, 2 were tuberculous meningitis, and 1 each were mediastinal, renal, gastrointestinal, and pleural tuberculosis. There was a high rate of anergy; only 6 of 15 patients tested had positive skin test results for tuberculosis. Of 11 tested for HIV, 7 were positive. There was a high rate of complications: preterm labor in five, fetal growth restriction in five, and oligohydramnios in one. One infant with growth restriction also had fetal ascites and was delivered at 33 weeks of gestation. One HIV-infected mother with severe pulmonary tuberculosis died of respiratory failure after a cesarean delivery for fetal distress. It is unclear whether the high rate of complications was due to tuberculosis alone, to the combination of tuberculosis and HIV, or to other factors. All women were treated with multiple-drug regimens (14 with isoniazid, ethambutol, and rifampin; 2 also with pyrazinamide, for CNS infection and for persistent positive sputum cultures on the three drugs). Because all the women had negative cultures by delivery, infants did not receive prophylaxis except for one whose mother had tuberculous meningitis. There were no cases of true congenital tuberculosis reported.

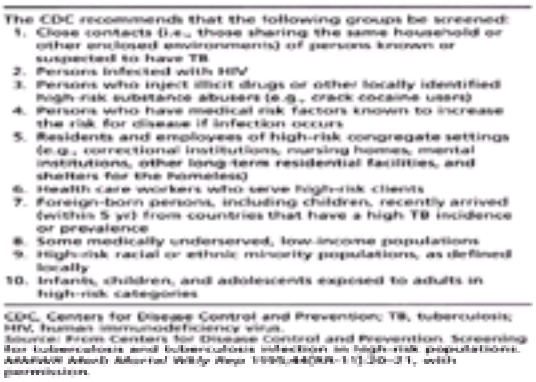
Diagnosis

As noted in the series discussed already, diagnosis of tuberculosis in pregnancy may be difficult, because a high percentage of patients are anergic and seek care late (3). Demonstration of acid-fast bacilli in sputum smears should raise suspicion, but culture confirmation is required for diagnosis, because sputum may contain nontuberculous mycobacteria. Diagnosis of extrapulmonary tuberculosis may be more difficult because specimens of urine and cerebrospinal fluid (CSF) are less frequently positive for acid-fast bacilli on smears (3). Demonstration of *Mycobacterium tuberculosis* in culture is thus mandatory for the definitive diagnosis, but treatment should be initiated with first-line drugs when there is an abnormal chest x-ray and suggestive clinical findings, particularly in high-risk groups.

Pregnancy does not appear to increase acquisition or activation of tuberculosis in

HIV-infected pregnant women (3).

No special recommendations have been made for tuberculosis screening in pregnancy, but recent CDC recommendations for screening high-risk populations include some pregnant women (6). These recommendations are summarized in Table 16.19.



The CDC recommends that the following groups be screened:

1. Close contacts (i.e., those sharing the same household or other enclosed environments) of persons known or suspected to have TB
2. Persons infected with HIV
3. Persons who inject illicit drugs or other locally identified high-risk substance abusers (e.g., crack cocaine users)
4. Persons who have medical risk factors known to increase the risk for disease if infection occurs
5. Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, mental institutions, other long-term residential facilities, and shelters for the homeless)
6. Health-care workers who serve high-risk clients
7. Foreign-born persons, including children, recently arrived (within 5 yr) from countries that have a high TB incidence or prevalence
8. Some medically underserved, low-income populations
9. High-risk racial or ethnic minority populations, as defined locally
10. Infants, children, and adolescents exposed to adults in high-risk categories

CDC, Centers for Disease Control and Prevention; TB, tuberculosis; HIV, human immunodeficiency virus.

Source: From Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations. *MMWR Morb Mortal Wkly Rep* 1995;44(RR-11):29–31, with permission.

TABLE 16.19. CDC RECOMMENDATIONS FOR TUBERCULOSIS SCREENING IN HIGH-RISK POPULATIONS

The CDC has provided revised guidelines for interpretation of tuberculin-skin tests (11) (Table 16.20).

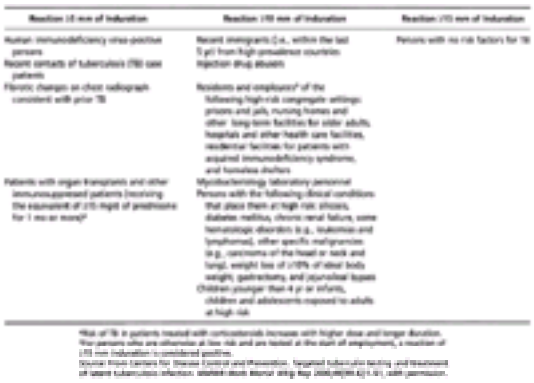


TABLE 16.20. CRITERIA FOR TUBERCULIN POSITIVITY, BY RISK GROUP

Congenital Tuberculosis

Congenital tuberculosis is rare, with less than 300 cases reported. Before two cases reported in 1994, the last reported case in the United States was in 1982. The

frequency has ranged from 3 cases among 100 infants of mothers with active tuberculosis to no cases in two series of 260 and 1,369 infants (2). In 29 cases of congenital tuberculosis reported since 1980, the median age of presentation was 24 days (range, 1 to 84), and common presenting findings were hepatosplenomegaly in 76%, respiratory distress in 72%, fever in 48%, lymphadenopathy in 38%, abdominal distention in 24%, lethargy or irritability in 21%, ear discharge in 17%, and papular skin lesions in 14%. Chest x-rays were abnormal in 23 infants, and skin test results at the time of diagnosis were negative in all 9 tested. Only 12 mothers had active tuberculosis; 15 were asymptomatic and were diagnosed only after their infants were diagnosed. Mortality from congenital tuberculosis was striking: 38% overall and 22% (5 of 23) of infants treated with chemotherapy. The observation that congenital tuberculosis commonly occurs in infants of asymptomatically infected mothers reinforces the need for careful evaluation of mothers of infants with suspected congenital infection.

On the basis of this review, Cantwell et al. (2) proposed revised diagnostic criteria for the diagnosis of congenital tuberculosis. The infant must have proven tuberculous lesions and at least one of the following: (a) lesions in the first week of life; (b) a primary hepatic complex or caseating hepatic granulomas; (c) tuberculous infection of the placenta or the maternal genital tract; or (d) exclusion of the possibility of postnatal transmission by a thorough investigation of contacts. They proposed that different restriction-fragment-length polymorphisms in the isolates from mother and infant would exclude congenital infection, but that identical patterns could also come from either congenital or postnatal infection.

Treatment Of Latent Tuberculosis Infection

The mainstay of treatment of latent tuberculosis infection in the United States over the past three decades has been isoniazid for 6 to 12 months (1). However, because of poor adherence and concerns about toxicity, there has been interest in the development of shorter rifampin-based regimens as alternatives to isoniazid for treatment of latent tuberculosis. In June 2000, the CDC provided revised recommendations for the treatment of latent tuberculosis. Four regimens are recommended for the treatment of nonpregnant adults with latent tuberculosis. These four regimens, together with their rating and evidence, are summarized in Table 16.21. Details of the medications used to treat latent tuberculosis, including doses, toxicities, and monitoring requirements, are shown in Table 16.22 and Table 16.23. Highlights of the recommended drug regimens for treatment of latent tuberculosis in pregnancy are summarized in Box 16.3 (1).

Rating[a] (Evidence)[b]			Rating	
Drugs	Duration (Mon)	Interval	HIV-	HIV+
Isoniazid	9	Daily	A (I)	A (I)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin-pyrazinamide	2	Daily	B (II)	A (I)
	2-3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (II)

[a]A, preferred; B, acceptable alternative; C, offer when A and B cannot be given.
[b]I, randomized clinical trial data; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.
Source: (From Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep 2000;49(RR-6):1–51, with permission.

TABLE 16.21. REGIMENS FOR TREATMENT OF ADULTS WITH LATENT TUBERCULOSIS INFECTION

TABLE 16.22. MEDICATIONS TO TREAT LATENT TUBERCULOSIS INFECTION: DOSES, TOXICITIES, AND MONITORING REQUIREMENTS

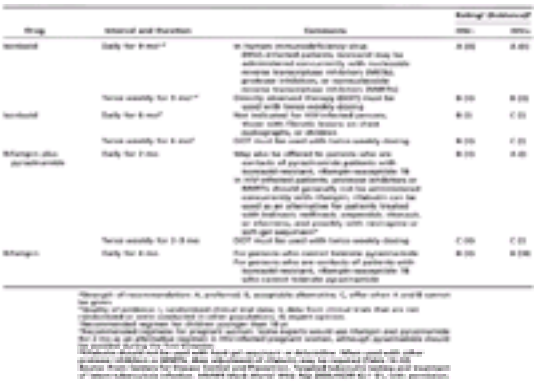


TABLE 16.23. RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS (TB) INFECTION IN ADULTS

Thus, for pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is recommended. The CDC recommends that for women at risk for progression of latent tuberculosis to active disease, particularly 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 during the first trimester. For women whose risk of active tuberculosis is lower, some experts recommend waiting until after delivery to start treatment.

Pregnancy has minimal influence on the pathophysiology of tuberculosis or the likelihood of its progression to active disease (1). The CDC notes that the current classification scheme for determining the tuberculin skin test is likely valid in pregnancy. The CDC further notes that there is no evidence that the tuberculin skin test has adverse effects on the pregnant mother or the fetus.

Pregnant women should be targeted for tuberculin skin testing only if there has been a specific risk factor for latent tuberculosis or for progression of latent tuberculosis to disease. Whereas the need for treatment of active tuberculosis during pregnancy is unquestioned (see later discussion), the treatment of latent tuberculosis in pregnancy has remained somewhat controversial. Thus, some experts recommend delaying treatment until after delivery because pregnancy itself does not increase the risk of progression and because women in pregnancy and the early puerperium may be more susceptible to isoniazid-induced hepatotoxicity. On the other hand, in view of the concern regarding progression of latent tuberculosis to disease and its effect on the mother and fetus, many experts agree that pregnant women with latent tuberculosis should be treated during pregnancy and have careful clinical and laboratory monitoring. It is felt that the risk of isoniazid-induced hepatotoxicity must be weighed against the risk of developing active tuberculosis and the consequences for the mother and fetus.

As noted already, the preferred treatment regimen for latent tuberculosis in pregnancy is isoniazid administered either daily or twice weekly. Whereas rifampin is probably safe, there are no efficacy data to support its use in pregnancy. The CDC notes clearly that for women at high risk for progression of latent tuberculosis to active disease, particularly those who are infected with HIV or who have recently been infected, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For these women, however, careful clinical and laboratory monitoring for hepatitis should be undertaken (Table 16.22). Pregnant women taking isoniazid should receive pyridoxine supplementation at 50 mg per day.

There have been no reported adverse effects of antituberculosis medications to infants who have been breast-feeding while mothers have taken them. Thus, breast-feeding is not contraindicated when the mother is being treated for latent tuberculosis. Yet infants whose breast-feeding mothers are taking isoniazid should receive supplemental pyridoxine. The amount of isoniazid provided by breast milk is inadequate for the treatment of the infant. The June 2000 guidelines recommended for pregnant women, as for other adults, that there should be targeted tuberculin skin testing (1). The target in tuberculin testing for latent tuberculosis infection is a strategic component of tuberculosis control that identifies persons at high risk for developing tuberculosis who would benefit by treatment of latent tuberculosis if detected. New recommendations indicate that persons with increased risk for developing tuberculosis include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions that are associated with an increased risk of progression from latent to active tuberculosis. These conditions are as follows: recent tuberculosis, particularly when it occurs within the past year, HIV infection, injection drug abuse, silicosis, radiographic findings consistent with prior tuberculosis, being underweight, diabetes mellitus, chronic renal failure or hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant (particularly renal or cardiac), and carcinoma of the head or neck. Combined with this recommendation, targeted tuberculin testing should be conducted only among

groups at high risk and discouraged in low risk. Infected persons who are considered to be at high risk for developing active tuberculosis should be offered treatment of latent tuberculosis irrespective of age. Cutpoints for defining a positive tuberculin skin reaction are shown in Table 16.20. In summary, for persons who are at the highest risk of developing active tuberculosis if they are infected with *M. tuberculosis,* more than or equal to 5 mm of induration is considered positive. For other persons with an increased probability of recent infection or with clinical conditions that increase the risk of progression to tuberculosis, more than or equal to 10 mm of induration is considered positive. For persons at low risk for tuberculosis for whom tuberculin testing is no longer generally indicated, more than 15 mm of induration is considered positive. Because of the complexity of this decision making, the reader is referred to the full CDC recommendations (1). The changes from prior recommendations on tuberculin testing and treatment of latent tuberculosis are summarized in Table 16.24.

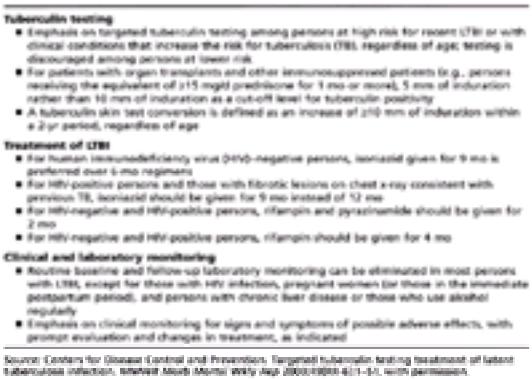
Box 16.3

Recommended drug regimens for latent tuberculosis infection in pregnancy are as follows:

In pregnancy, the preferred regimens include

- Isoniazid daily for 9 months or
- Isoniazid twice weekly for 9 months or
- Isoniazid daily for 6 months or
- Isoniazid twice weekly for 6 months as shown in Table 16.23.

Note that some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen for HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.



Tuberculin testing

- Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for tuberculosis (TB); regardless of age; testing is discouraged among persons at lower risk
- For patients with organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of ≥15 mg/d prednisone for 1 mo or more), 5 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity
- A tuberculin skin test conversion is defined as an increase of ≥10 mm of induration within a 2-yr period, regardless of age

Treatment of LTBI

- For human immunodeficiency virus (HIV)-negative persons, isoniazid given for 9 mo is preferred over 6-mo regimens
- For HIV-positive persons and those with fibrotic lesions on chest x-ray consistent with previous TB, isoniazid should be given for 9 mo instead of 12 mo
- For HIV-negative and HIV-positive persons, rifampin and pyrazinamide should be given for 2 mo
- For HIV-negative and HIV-positive persons, rifampin should be given for 4 mo

Clinical and laboratory monitoring

- Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI, except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly
- Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment, as indicated

Source: Centers for Disease Control and Prevention. Targeted tuberculin testing treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep 2000;49(RR-6):1-51, with permission.

TABLE 16.24. CHANGES FROM PRIOR RECOMMENDATIONS ON TUBERCULIN TESTING AND TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)

Treatment Of Active Tuberculosis

Emergence of tuberculous isolates with multidrug resistance has prompted revised treatment recommendations from the CDC (4). In New York City, 33% of cases showed resistance to at least one drug, and 19% were resistant to both isoniazid and rifampin. Treatment regimens for children and nonpregnant adults are shown in Table 16.25 and Table 16.26. The initial regimens include four drugs for the first 2 months, followed by an altered regimen based on drug susceptibility testing.

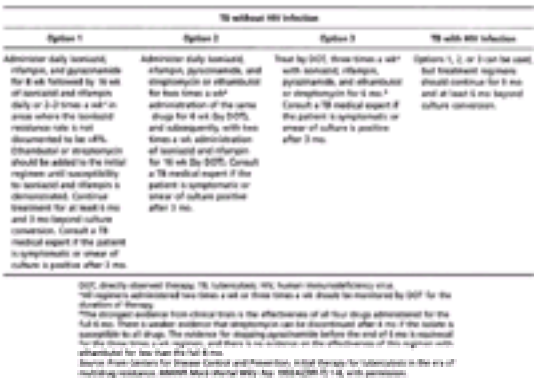


TABLE 16.25. REGIMEN OPTIONS FOR INITIAL TREATMENT OF TB IN CHILDREN AND NONPREGNANT ADULTS

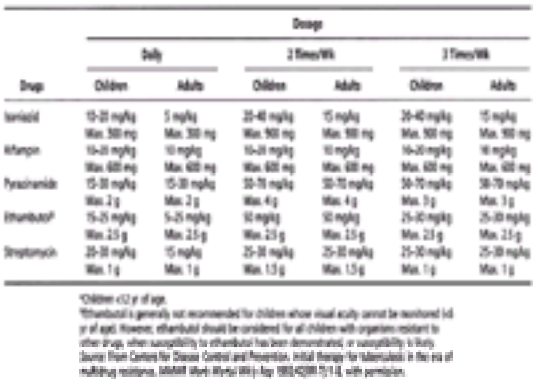


TABLE 16.26. DOSAGE RECOMMENDATION FOR THE INITIAL TREATMENT OF TB AMONG CHILDREN[a] AND ADULTS

Special consideration is given to the treatment of tuberculosis in pregnancy. Effective therapy is essential, but streptomycin may cause congenital deafness. Routine use of pyrazinamide is not recommended during pregnancy because the risk of teratogenicity has not been determined. A minimum of 9 months of therapy is

recommended because the 6-month regimens cannot be used. Thus, in pregnancy, the initial regimen is isoniazid plus rifampin, and ethambutol, if potential isoniazid resistance is suspected. If sensitivities prove all drugs to be effective, treatment may be given twice weekly after the first 2 months. Breast-feeding should not be discouraged for women taking these drugs (Box 16.4) (5).

Box 16.4

Recommended initial treatment regimen for active tuberculosis in pregnancy is as follows:

- Isoniazid, 300 mg daily, plus rifampin, 600 mg daily.
- Add ethambutol, 2.5 g daily, if there is potential isoniazid resistance
- All drugs for a minimum of 9 months.
- Give pyridoxine, 50 mg daily with isoniazid

Note that pyrazinamide is not recommended during pregnancy because teratogenicity has not been assessed. Streptomycin may cause congenital deafness.

In an extensive review, Snider et al. (8) provided data on ethambutol, isoniazid, streptomycin, and rifampin. Ethionamide is the only antituberculous agent considered clearly teratogenic, but it is rarely indicated.

Ethambutol has replaced *p*-aminosalicylic acid as a first-line drug. It is easier to tolerate, and there is no evidence of adverse fetal effects (8). On the basis of more than 600 cases, Snider et al. (8) considered ethambutol safe for use in pregnancy.

Isoniazid also has no special adverse effects in the pregnant woman or the fetus. Of 1,480 pregnancies in which isoniazid was used, there were only 16 abnormal fetuses—a rate lower than that in the general population (8).

Streptomycin, when used for periods of several weeks in the treatment of maternal tuberculosis, commonly causes eighth nerve damage in exposed fetuses (9). Snider et al. (8) reported eighth nerve damage in 15% of infants exposed *in utero* to streptomycin in the treatment of maternal tuberculosis.

The overall risk of congenital anomalies does not seem to be increased in fetuses with *in utero* exposure to rifampin. Fetal malformations have been seen in 14 of 442 women (8). The anomalies covered a wide spectrum, suggesting no cause-effect relationship.

PROTOZOA

Toxoplasmosis

Toxoplasmosis is a widely distributed illness, caused by *Toxoplasma gondii,* an intracellular parasite. In the last few years, there has been renewed interest in this

infection because of four developments: growing numbers of patients with acquired immunodeficiency syndrome (AIDS) who are particularly susceptible to toxoplasmosis, particularly severe manifestations; an FDA initiative in food safety; concerns about current diagnostic techniques; and availability of prenatal diagnosis.

Epidemiology

Although *T. gondii* is found in many mammalian species, the cat is the only definitive host. This parasite may exist in three forms (trophozoite, cyst, or oocyst). Trophozoites are the invasive forms, and the cysts are the latent forms. The oocysts are found only in cats. Human infection may be acquired by consuming raw or undercooked meat of infected animals (particularly mutton and lamb) or by contact with oocysts from the feces of an infected cat. The oocysts may be spread to humans or to food by hand or by insects. Cats acquire toxoplasmosis by eating infected mice or other animals. Oocysts in cat feces do not become infective for 4 to 5 days. Once infected by oocysts from cat feces or by cysts from infected meat, persons may experience a parasitemia, during which fetal involvement may occur. Later, *T. gondii* cysts appear in tissues, particularly striated muscle and brain, where they persist indefinitely.

In the general population, the seroprevalence of *Toxoplasma* varies widely, from approximately 55% in France to 26% in Denmark to 10% in the United States among military recruits (1). Among pregnant women, recent data from the United States (1988 to 1994) show that the current seroprevalence is only 14% (Table 16.27). Older data in the United States showed a seroprevalence of 20% to 40% (2), whereas in Paris, the prevalence was up to 84% (3). Thus, compared with western Europeans, Americans have lower seroprevalence. In addition, seroprevalence in the United States appears to have decreased in the general population in the last 30 years, as judged by seroprevalence in military recruits.

	Percent
Seroprevalence	3–30%
Acute maternal infection in pregnancy	
Urban Alabama	0.06% (2/5,142)
United States (estimated)	0.2–1%
Acute congenital infection	
New England	0.01% (52/600,000)
United States (estimated)	0.01–0.1%

Sources: From Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis* 1994;18:853–861; Hunter K, Slagno S, Capps E, et al. Prenatal screening of pregnant women for infections caused by cytomegalovirus, Epstein-Barr virus, herpesvirus, rubella, and *Toxoplasma gondii*. *Am J Obstet Gynecol* 1983;145:269–273; and Guerina NG, Hsu HW, Meissner HC, et al. Neonatal serologic screening and early treatment for congenital *Toxoplasma gondii* infection. *N Engl J Med* 1994;330:1858–1863, with permission.

TABLE 16.27. EPIDEMIOLOGY OF TOXOPLASMOSIS IN THE UNITED STATES

Domestic cats acquire the infection as early as 6 to 10 weeks of age. Once infected, they excrete the oocysts for a short period of time (approximately 1 to 2 weeks) and usually are seronegative while shedding occurs. The duration of immunity in cats is

uncertain but is estimated to be from approximately $^{1}/_{2}$ a year to up to 6 years.

Consumption of infected food may be another source of toxoplasmosis. In the United States, the greatest source of food-related transmission is meat from infected pigs. However, the seroprevalence in pigs is decreasing and is now only approximately 2.5% in pigs sold for market, in comparison to seroprevalence rates of 24% approximately two decades ago (1).

Overall risk factors for seroprevalence for toxoplasmosis in the United States include increasing age (older than 30 to 40 years), less than a high school education, rural or small town residence, and foreign birth.

Rates of seroconversion in pregnancy also vary widely on a geographic basis. In France, the rate of infection in pregnancy is 1.5%, whereas in the United States, it is estimated that the rate is 0.2% to 1%. In 1983, the seroconversion rate in urban Alabama was only 0.06% (2 of 5,142) (1,4,5).

Rates of congenital infection with toxoplasmosis have been reported for western Europe and the United States. In France, the rate is approximately 0.2%. In New England, a recent study showed the rate was 0.01% (52 cases of 600,000 births), whereas estimates for the overall United States placed the rate at 0.01% to 0.1%. This estimate would project to approximately 400 to 4,000 cases per year in the United States (1,5,6). Recent data have clarified the risk of fetal infection when there is primary toxoplasmosis in pregnancy. Clearly, the risk of fetal infection increases with gestational age; that is, the later in pregnancy toxoplasmosis infection occurs, the more frequently the fetus is infected. As shown in Fig. 16.7, when there is no maternal treatment, the rate of fetal infection rises from approximately 10% in the first trimester to 30% in the second trimester to 60% in the third trimester. When there are seroscreening and treatment programs, the rate of fetal infection is reduced by more than 50%. Figure 16.7 displays the rate of congenital infection by gestational age of maternal infection in more than 2,000 pregnancies. When maternal infection occurred in the first 2 weeks of pregnancy, the fetal infection rate was 0. Thereafter, the rate of fetal infection continued to climb as gestation advanced (Fig. 16.8). Further, these are rates that occur when there are seroscreening and maternal treatment programs. However, when fetal infection occurs in the first trimester, it is likely to be severe or to lead to stillbirth, whereas with fetal infection later in gestation, the consequences are less severe. Classic data from France are shown in Table 16.28 (7). Figure 16.9 shows severe hydrocephalus in a stillborn infant with congenital toxoplasmosis.

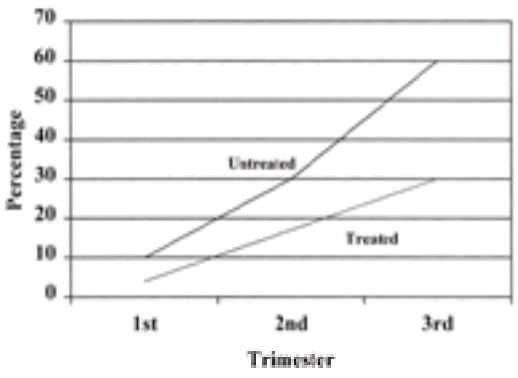


FIGURE 16.7. Incidence of fetal infection by trimester of maternal infection. Note that mothers were treated with spiramycin (3 g per day).

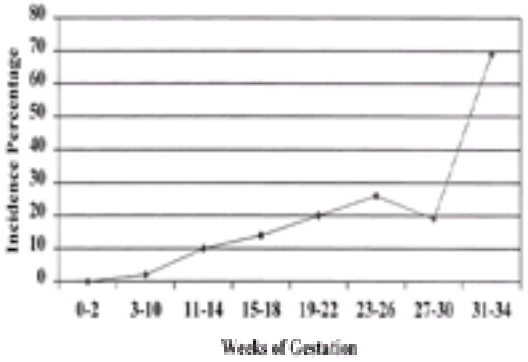


FIGURE 16.8. Congenital toxoplasmosis by time of maternal infection in 2,281 pregnancies.

Trimester	% Infected	% Severe or Stillborn
1st	13	75
2nd	30	20
3rd	60	0

Source: From Desmont G, Couveur J. Congenital toxoplasmosis. A prospective study of 378 pregnancies. *N Engl J Med* 1974;290:1110, with permission.

TABLE 16.28. FETAL INFECTION AFTER PRIMARY MATERNAL TOXOPLASMOSIS

FIGURE 16.9. Severe hydrocephalus in a stillborn infant with congenital toxoplasmosis.

Congenital infection does not affect more than one infant in a particular mother (8). The role of toxoplasmosis in chronic abortion remains unresolved after 20 years of study.

Diagnosis

Subclinical disease is the rule in both adults and newborns with toxoplasmosis. When it is apparent clinically in a normal host, the most common manifestation is lymphadenopathy (most commonly cervical). Fever, fatigue, sore throat, maculopapular rash, and occasionally hepatosplenomegaly may also be noted. Examination of the peripheral blood shows lymphocytosis or an occasional atypical lymphocyte. Accordingly, this disease is often thought to be the “flu” or infectious mononucleosis. An occasional adult may have mainly ocular symptoms including haziness of vision, pain, and photophobia. In these cases, ophthalmologic examination shows clusters of yellow-white patches in the optic fundus, representative of a focal necrotizing retinochoroiditis. In healthy adults, clinical toxoplasmosis is mild and self-limited; in immunosuppressed individuals such as those with AIDS, it leads to serious pulmonary or CNS involvement.

As noted, most infants with congenital toxoplasmosis have only serologic abnormalities. Of those with clinical disease, few have the commonly suggested triad of intracerebral calcifications, chorioretinitis, and hydrocephaly in the past. Findings from a recent French series are shown in Table 16.29, where we see that of 210 infants with congenital infection diagnosed during a study of infection in pregnancy, most (55%) had subclinical infection. Thus, there is a wide spectrum of disease. Acute primary toxoplasmosis in pregnancy has also been associated with abortion, prematurity, and growth retardation.

Subclinical pattern	55%
Chorioretinitis	22%
Intracranial calcifications	11%
Intrauterine growth retardation	6%
Microcephaly	5%
Low birthweight	4%
Hepatosplenomegaly	4%
Hydrocephaly	4%

[a]Diagnosed via study of pregnant women.
Source: From Couvreur J, Thulliez P, Daffos F. Toxoplasmosis. In: Charles D, ed. *Kass handbook of infectious disease obstetric and perinatal infections*. St. Louis: Mosby-Year Book, 1993, with permission.

TABLE 16.29. SELECTED CLINICAL FINDINGS IN CONGENITAL TOXOPLASMOSIS (N = 210)[a]

Numerous diagnostic approaches are used for toxoplasmosis, as shown in Table 16.30. Toxoplasmic cysts may be identified histologically in infected tissue such as lymph nodes, but this technique is cumbersome and probably of limited sensitivity. In selected laboratories, *T. gondii* may be cultured either using tissue culture (such as in mouse fibroblasts) or by peritoneal inoculation of mice. Recent modifications of the mouse inoculation method include assay of mouse serum 6 weeks after inoculation for *Toxoplasma*-specific antibody by EIA. Tissue culture is faster, but mouse inoculation is more sensitive. *Toxoplasma* antigens may also be demonstrated by immunofluorescent techniques, but these also probably have limited sensitivity.

- Histologic identification of cyst
- Isolation of *Toxoplasma gondii*: tissue culture—more rapid; mouse inoculation—more sensitive
- Immunofluorescent identification
- Serologic detection (IgG, IgM)—eight tests used
- *Toxoplasma* DNA via PCR—new
- Nonspecific tests

IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

TABLE 16.30. DIAGNOSIS OF TOXOPLASMOSIS

Serologic techniques are generally used to detect toxoplasmosis: at least eight different techniques including EIA, indirect fluorescent antibody, complement fixation, and the “classic” Sabin-Feldman dye test (8). IgG antibodies peak within 1 to 2 months of the onset of infection, and low titers persist for years. IgM antibodies appear within a week and usually last for a few months. Commercially available kits for diagnosis of *Toxoplasma*-specific IgG are generally reliable, but the FDA has

issued a Public Health Advisory regarding the limitations of *Toxoplasma*-specific IgM in commercial kits (10). Specifically, physicians were advised to interpret results “with caution.” Further, physicians were advised that they should not rely on any single test in diagnosing recent infection and in deciding medical action. The concern was with false-positive *Toxoplasma* IgM leading to false-positive diagnosis of recent toxoplasmosis and hence the likelihood of fetal infection. Thus, it is complicated to make the diagnosis of recent toxoplasmic infection. Often, multiple samples are needed. It is possible to make the diagnosis, but there are still some false-positives even in expert laboratories. Physicians are advised to consult an expert in making the diagnosis (1). Advice on the diagnosis may be obtained from the FDA or from the laboratory at Stanford University (laboratory of Dr. Jack Remington).

Thus, serologic results for *Toxoplasma* antibodies should not be accepted at face value from all laboratories because accuracy varies among laboratories. Some commercial facilities do not store serum for more than a few days. This practice is most unfortunate, because repeated testing and running the acute and convalescent serum in parallel are often needed to make the diagnosis. The clinician is advised to use a reliable laboratory and to know how to interpret its results. Otherwise, incorrect information and incorrect counseling may result (11).

New diagnostic techniques employing DNA testing have been developed (such as PCR detection in amniotic fluid). These diagnostic approaches have shown rapid and sensitive identification of the infected fetus.

In 1988, Daffos et al. (12) first reported prenatal diagnosis of 746 pregnancies at risk for congenital toxoplasmosis based on culture of fetal blood and amniotic fluid for *T. gondii,* testing of fetal blood for specific IgM and for nonspecific measures for infection (including platelet count, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, lactate dehydrogenase, white blood cell count, eosinophilia, and total IgM), and fetal ultrasound examination. Overall, infection was diagnosed in 39 (93%) of 42 fetuses.

Subsequent series have confirmed the validity of diagnosis *in utero* (13).

In 89 cases of proven fetal toxoplasmosis, ultrasound abnormalities have been cataloged. Of these cases, 32 (36%) showed abnormal findings: ventricular dilation, 25; intracranial densities, 6; placental thickness (higher than the 95th percentile), 11; placental hyperdensity, 2; intrahepatic densities, 4; hepatomegaly, 2; ascites, 5; pericardial effusion, 2; and pleural effusion, 1 (14).

With the advent of PCR, rapid diagnosis of congenital toxoplasmosis has been reported. In 1990, Grover et al. (15) described a study of 43 documented cases of acute maternal infection in which PCR was compared with standard methods. PCR correctly identified five of five samples of amniotic fluid from four proven cases of congenital infection. There were no false-positive diagnoses reported by any of the methods. Thus, detection of *T. gondii* in amniotic fluid by PCR appeared to be very promising, particularly because it is rapid and highly sensitive.

In a larger series from Paris, Hohlfeld et al. (16) compared PCR on amniotic fluid with their “classic” methods of ultrasonography, amniocentesis, and fetal blood sampling. In 2,632 cases of maternal infection, the overall risk of congenital infection was 7.3%, varying from 2% in weeks 3 to 10, to 22% in weeks 27 to 30, to 67% in

weeks 31 to 34. There was no observed risk of congenital infection among 100 women with infection during the 2 weeks after the last menstrual period. In 339 cases, PCR on amniotic fluid was used. Overall, the classic diagnostic methods had a sensitivity of 92%, specificity and positive predictive value of 100%, and a negative predictive value of 99.4%. With PCR, the sensitivity, specificity, and predictive values were all 100%. The authors concluded that *in utero* diagnosis of congenital toxoplasmosis may be simplified because fetal blood sampling has been replaced by PCR of amniotic fluid and inoculation of amniotic fluid into mice. This new approach also offers safer and faster results.

Further data on the reliability of diagnosis of congenital toxoplasmosis have recently been reported from a retrospective study from six reference centers in Europe, where amniocentesis and cordocentesis were used in 122 patients between 1986 and 1996. The diagnosis of congenital toxoplasmosis was based on the persistence of specific IgG at age 1 year or reappearance of specific IgG in the child after cessation of therapy. Overall, the most sensitive diagnostic combination was amniotic fluid PCR plus amniotic fluid mouse inoculation. Fetal blood tests were much less sensitive (Table 16.31). Thus, amniotic fluid PCR has been confirmed as the single most reliable test, but the combination of amniotic fluid PCR and amniotic fluid mouse inoculation achieves a sensitivity of more than 90%.

Test	Sensitivity (%)	Specificity (%) (1—False-Positive)
AF mouse inoculation	58	98
AF-PCR	81	96
Both of above	91	88
Fetal blood tests[a]	31–47	95–100

AF, amniotic fluid; AF-PCR, amnionic fluid polymerase chain reaction.
[a]Included mouse inoculation, IgM and IgA antibodies.
Source: From Foulon W, Pinon JM, Stray-Pedersen B, et al. Prenatal diagnosis of congenital toxoplasmosis: a multicenter evaluation of different diagnostic parameters. Am J Obstet Gynecol 1999;181:843–7, with permission.

TABLE 16.31. PRENATAL DIAGNOSIS OF CONGENITAL TOXOPLASMOSIS

An alternative to *in utero* diagnosis is early neonatal diagnosis and prompt treatment (6). In Massachusetts and New Hampshire, newborns were screened for intrauterine infection with *T. gondii* by an immunoassay performed on routinely collected blood. If the screening test result was positive, confirmatory testing was performed for specific IgG and IgM antibodies in maternal and neonatal serum. Infants with serologic evidence of infection had 1 year of treatment and detailed clinical follow-up. Treatment consisted of combinations of pyrimethamine, sulfadiazine, and folinic acid (leucovorin), but five different regimens were used at the discretion of attending physicians. Spiramycin was also given to two infants. Among 635,000 screened infants, 100 had positive screening test results, and 52 (1 of 12,211) had confirmed infection. Fifty infants were identified only through neonatal screening (not by initial clinical examination). More detailed clinical evaluation, performed after serologic results were available, showed abnormalities of the eyes or CNS in 19 (40%) of 48

infants. Yet, after treatment, only 1 of 46 children had any neurologic deficit. Of 39 treated children with follow-up eye examinations, 4 (10%) had lesions that may have developed postnatally. Treatment in the children was well tolerated in 32 of 47 for whom toxicity information was available. The remaining infants had mild anemia, leukopenia, or rash. All infants had normal growth. The estimated cost per case identified was less than $30,000, an amount considered reasonable in view of the costs of rearing an afflicted child. Thus, routine neonatal screening for toxoplasmosis, coupled with early treatment, may reduce long-term sequelae, and this approach may be more practical than *in utero* diagnosis and treatment in the United States, where the incidence is low. However, a limitation of the approach of screening newborns is that this misses the diagnosis in severely affected fetuses who wind up with either abortion or stillbirth.

Prevention

To prevent toxoplasmosis in pregnancy, most authorities advise (a) avoiding undercooked meat; (b) hand washing after handling a cat, particularly before eating; (c) having someone else change the litter box daily; (d) not permitting indoor cats to go outside, where they may attack an infected mouse; (e) not allowing stray cats in the house; and (f) not feeding raw meat to cats. Based on their data in Alabama, Hunter et al. (4) did not favor routine serologic screening programs in view of the expense of screening many women who are susceptible and the low attack rate. Alternatively, patient education is recommended by Frenkel (18). Wilson and Remington (19), however, note that regional programs are needed in the United States to provide data pertinent in this country.

Recently, Foulon et al. (20) reported that the impact of primary prevention of congenital toxoplasmosis by hygienic measures was limited. They noted that such a program in Brussels, Belgium, only reduced the seroconversion rate for acquisition of toxoplasmosis in pregnancy from 1.43% to 0.95% (not a statistically significant decrease). Whether such an effort would significantly reduce the seroconversion rate in the United States is not clear.

Treatment

For women with toxoplasmosis confirmed in the first trimester, the physician should offer counseling regarding the risk of serious congenital infection, the availability of *in utero* diagnosis, and pregnancy termination.

As noted, widespread screening and treatment programs are practiced in many western European countries. One treatment protocol is shown in Table 16.32. In brief, spiramycin treatment is begun when maternal diagnosis is made, and diagnostic evaluation of the fetus is begun after 18 weeks. If fetal diagnosis is confirmed, then treatment is begun with pyrimethamine plus sulfadiazine or termination is offered. When there is late infection (after 26 to 34 weeks), there is presumptive treatment with pyrimethamine and sulfadiazine without diagnostic workup. In late maternal infection, although there is a high risk of fetal infection, the likelihood of severe infection is small (1). Specific regimens available in the United States are shown in Box 16.5 (21). Note that treatment is available with pyrimethamine and sulfadiazine, but these should be accompanied by administration of folinic acid to pregnant women. In addition, spiramycin is available but only

through the FDA at the telephone number shown.

Box 16.5

Maternal treatment regimens for toxoplasmosis include the following (from Sever JL, 1998):

1. Pyrimethamine 25 mg orally daily (after first trimester) plus sulfadiazine 1 g orally four times a day for 28 days, followed by half dose for 28 days more
2. Also give 6 mg folinic acid intramuscularly or orally three times a week
3. Spiramycin may be used initially (available in the United States through the FDA, at 301-827-2335)

Early infection (before 26 wk)

1. Spiramycin when maternal infection diagnosed
2. Ultrasound and amniocentesis after 18 wk for fetal diagnosis
3. If AF-PCR result is positive, treat with pyrimethamine-sulfadiazine or termination

Late infection (after 26–34 wk)

1. Presumptive treatment with pyrimethamine-sulfadiazine without amniocentesis

AF-PCR, amnionic fluid polymerase chain reaction.
Source: From Tulliez P. (Paris) at CDC Workshop, Atlanta, GA, 1998, with permission. Proceedings not published.

TABLE 16.32. TREATMENT OF TOXOPLASMOSIS: FRENCH PROTOCOL

All authorities agree that symptomatic infants with congenital toxoplasmosis should be treated with sulfadiazine, pyrimethamine, and folinic acid supplementation. Details of the treatment regimens are available (8). In the infant with asymptomatic toxoplasmosis at birth, late CNS sequelae are possible. Based on the recent data from New England, early treatment of asymptomatically infected infants appears to reduce long-term sequelae (6).

LYME DISEASE

Since Lyme disease was first described in 1977, it has rapidly emerged as an important infection. In 1999 there were 16,273 Lyme disease cases reported to the CDC for an overall incidence of 6.0 per 100,000 population (1). This represents over a 30-fold increase in the less than 500 cases reported in 1982. Most cases were reported from the Northeast, mid-Atlantic, and north central regions, as well as California (Fig. 16.10). During 1999, the highest reported rates in the Northeast and north central areas were seen in Connecticut (98 per 100,000), (Rhode Island 55.1; New York 24.2; Pennsylvania 23.2; Delaware 22.2; New Jersey 21.2; Maryland 17.4;

Massachusetts 12.7; Wisconsin 9.3 [1]). The CDC suggested that the tremendous increase in reported Lyme disease cases since 1982 was due to four factors: (a) heightened awareness of Lyme disease by patients and physicians; (b) increased use of laboratory testing for the diagnosis of Lyme disease; (c) increased surveillance and health department requirements for reporting; and (d) a true increase in the number of cases (1). The latter reflects increasing penetration of suburban development into rural forest areas where deer are present in large numbers. Lyme disease is currently the most commonly reported vector-borne disease in the United States and now accounts for 90% of vector-borne infections reported to the CDC (1).

FIGURE 16.10. Reported cases of Lyme disease—United States, 1992. (From Centers for Disease Control. Lyme disease—United States, 1991–1992. *MMWR Morb Mortal Wkly Rep* 1993;42:345–348, with permission.)

Lyme disease is a tick-borne infection that is caused by the spirochete *Borrelia burgdorferi.* Lyme disease is a multisystem illness that is characterized by a distinct lesion, erythema chronicum migrans, which often is followed by neurologic, cardiac, and arthritic manifestations (2,3 and 4). The Lyme disease spirochete is transmitted by *Ixodes* ticks. The most common vector is the deer tick, *Ixodes dammini,* whose distribution coincides with endemic areas of the disease in the northeast United States. In the western United States, *Ixodes pacificus,* the black-legged deer tick, is responsible for transmission of disease. The white-footed mouse is host for the larval and nymph stages of the disease. White-tailed deer are the preferred hosts for the adult-stage *I. dammini.* Most human infections with *B. burgdorferi* occur from May through August, a time when both nymphal-stage activity and human outdoor activity are at their highest (4).

As noted by Steere (4), Lyme disease generally occurs in stages characterized by differing clinical manifestations. The initial manifestation is erythema migrans, which is followed several weeks or months later by meningitis or Bell palsy and subsequently followed months or years later by arthritis. Asbrink and Hovmark (5) suggested a classification based on the system used in syphilis, in which Lyme disease is divided into early and late infection. Early infection consists of stage I (localized erythema migrans), followed within days or weeks by stage II (disseminated infection), and within weeks or months by intermittent symptoms. Late

infection, or stage III (persistent infection), begins generally a year or more after the onset of disease.

Shapiro et al. (6) recently assessed the risk of infection with *B. burgdorferi* and the efficacy of prophylactic antimicrobial treatment after a deer tick bite. Of the 344 deer ticks studied, only 15% were infected with *B. burgdorferi,* as analyzed by PCR technology (6). Erythema migrans was noted in only two patients, both of whom were in the placebo group (6). The risk of infection in the placebo-treated patients was 1.2% (95% CI, 0.1–4.1%).

After transmission of *B. burgdorferi,* approximately 60% to 80% of individuals develop erythema migrans. This lesion begins as a small erythematous papular macule, which is then followed by a gradual centrifugal expansion over 3 to 4 weeks. In general, the lesions clear centrally and take on an annular configuration that averages 15 cm in diameter. The initial skin lesion is often accompanied by systemic symptoms including fever, flulike symptoms with migratory arthralgias, myalgias, headaches, and regional lymphadenopathy (4). Even without treatment, erythema migrans usually fades within 3 to 4 weeks.

Stage II early infection, or disseminated infection, occurs within days or weeks after transmission. Disseminated infection is often associated with characteristic symptoms involving skin, nervous symptoms, or the musculoskeletal system. Nearly half the patients will develop secondary annular skin lesions that resemble the primary erythema migrans lesions. These are usually smaller and migrate less. Patients commonly develop severe headaches and mild stiffness of the neck, which occur in short attacks. Interestingly, a recent report using PCR assay for *Borrelia*-specific DNA has demonstrated the presence of *B. burgdorferi* in the CNS during acute disseminated infection (7). The musculoskeletal pain associated with Lyme disease is migratory, lasting only hours or days in any given location; it may involve the joints, bursa, tendons, muscle, and bone. During the disseminated stage, patients frequently have severe malaise and fatigue. As the infection begins to localize, approximately 15% to 20% of patients develop frank neurologic involvement. The classic triad of neurologic Lyme disease includes meningitis, cranial nerve palsies, and peripheral radiculopathies. The predominant symptoms of Lyme meningitis are severe headaches and mild neck stiffness, which fluctuate for several weeks. Cerebral spinal fluid demonstrates a leukopoietic pleocytosis, slightly elevated protein levels, and normal glucose levels. Nearly one half of the cases of meningitis have an associated mild encephalitis that leads to loss of concentration, emotional lability, lethargy, sleep disturbances, or focal cerebral dysfunction. The most commonly affected cranial nerve is the seventh, leading to Bell palsy. One third of the patients with Bell palsy have bilateral involvement. Peripheral radiculopathies are characterized by severe neuritic pain, dysesthesia, focal weakness, and areflexia. Within several weeks of the onset of disease, 5% to 10% of patients have cardiac involvement. Fluctuating degrees of atrioventricular block are the most common abnormalities; this ranges from first-degree to complete heart block. Occasionally patients have acute myopericarditis, mild left ventricular dysfunction, or (rarely) cardiomegaly or fatal pancarditis. Cardiac abnormalities usually last from 3 days to 6 weeks. Approximately 6 months after the onset of disease, about 60% of the patients in the United States begin to have brief attacks of asymmetric oligoarticular arthritis, primarily in the large joints, particularly the knee.

Stage III, or late infection, is characterized by episodes of arthritis during the second

and third year of the illness, which often become chronic arthritis. Nocton et al. (8) recently used PCR to detect *B. burgdorferi* DNA in the synovial fluid of patients with Lyme arthritis. Nearly all joint fluid samples from untreated patients with Lyme arthritis contained detectable *B. burgdorferi* DNA, whereas most posttreatment samples and all control samples were negative (8). In addition, several late syndromes of the CNS have now been described. These include progressive encephalomyelitis (9), subacute encephalitis, dementia, and a syndrome suggesting demyelination.

Experience with Lyme disease during pregnancy is rather limited (10). Concern has arisen because other spirochetes such as *T. pallidum* cross the placenta and produce adverse effects on the fetus or neonate. In 1985, the first case of transplacental transmission of *B. burgdorferi* was documented by identification of the spirochete in multiple organs of an infant who died of congenital heart disease shortly after birth (11). Subsequently, Weber et al. (12) isolated the organism from the brain and liver of an infant who died within the first 24 hours of life. Both of these infants were born to mothers who had erythema migrans in the first trimester. Three stillbirths with recovery of *B. burgdorferi* from multiple organs subsequently were reported (13,14 and 15). The CDC evaluated the effect of Lyme disease during pregnancy on two occasions. In a retrospective study, the CDC identified five adverse outcomes in fetuses born to 19 women with Lyme disease (15). Among the adverse outcomes noted were prematurity, cortical blindness, fetal demise, syndactyle, and a rash in the neonate. However, they could not prove a teratogenetic pattern or show a reduction in fetal morbidity if the mothers had been appropriately treated for Lyme disease. In the second prospective study, the CDC evaluated 17 women with documented Lyme infection in the first trimester (16). Only two of these pregnancies were abnormal, with one resulting in a spontaneous abortion at 13 weeks. In the second, the infant had syndactyle. In a survey of core blood serum from 421 infants born in an endemic area for *B. burgdorferi,* Williams et al. (17) found no relationship between congenital malformation and the presence of antibody to Lyme disease. In a recent European study, 0.85% of core blood obtained from more than 1,400 pregnancies demonstrated elevated titers to *B. burgdorferi* (18). Of these, only one patient had clinical disease during her pregnancy, and her infant had a ventricular septal defect without other anomalies. In the remaining 11 infants with elevated IgG cord titers, 6 had abnormal neonatal courses; 2 with hyperbilirubinemia, 1 macrocephaly, 1 intrauterine growth retardation, and 1 supraventricular extrasystoles. However, at an average follow-up of 9 months, all of these latter six infants were normal. Thus, any relationship between positive IgG titers and abnormalities in the fetus or neonate is inconclusive. Recently, Strobino et al. (19) conducted a prospective study to determine whether prenatal exposure to Lyme disease was associated with an increased risk of adverse pregnancy outcome. Nearly 2,000 women were enrolled after completing a questionnaire and having serum tested for antibody to *B. burgdorferi* at their first prenatal visit and at delivery (19). These authors reported that neither maternal Lyme disease nor an increased risk of exposure to Lyme disease was associated with fetal death, decreased birthweight, or length of gestation at delivery (19). Tick bites or Lyme disease around the time of conception was not associated with congenital malformations (19).

The diagnosis of Lyme disease is hindered by the various manifestations of the disease. Culture or direct visualization of *B. burgdorferi* from patient specimens is difficult, so serology is currently the only practical laboratory diagnosis available. Indirect fluorescent antibody and ELISA are the most commonly used tests for the diagnosis of Lyme disease. In general, ELISA is preferred because of its increased

sensitivity and specificity. It is important to recognize that false-positive results can be seen with other spirochetal diseases, infectious mononucleosis, autoimmune disorders, and Rocky Mountain spotted fever. Thus, an indirect screening test for syphilis should be done on all patients with positive results to rule out syphilis. False-negative results may be seen early in the disease, that is, during the first 2 weeks when infection is localized to the skin, or if antibiotics have been given before an immune response can be mounted. Thus, most laboratories use a two-test approach for the serologic diagnosis of Lyme disease. Specimens are initially screened with the more sensitive ELISA or IFA. Positive (or equivocal) specimens are confirmed by the more specific IgG and IgM Western blot. The sensitivity and specificity of the ELISA and Western blot vary, depending on the time of specimen acquisition and, thus, clinical and exposure histories are important components of interpreting the serologic results.

Because laboratory diagnosis is uncertain, a case definition has been developed to aid in recognition of Lyme disease: (a) the occurrence of erythema migrans no more than 30 days after exposure in an endemic area (i.e., where vector ticks are known to exist) or (b) the involvement of at least one of the three commonly affected organ systems producing neurologic, cardiovascular, or arthritic systems; and either (c) a positive serology, (d) isolation of *B. burgdorferi,* or (e) erythema migrans or positive serology without a history of exposure. As noted already, the use of PCR technology to detect *B. burgdorferi* DNA in spinal fluid and synovial fluid may be useful in determining the natural history of Lyme disease and improving the reliability of the diagnosis. The diagnosis of Lyme disease has primarily been based on the presence of a characteristic clinical picture, exposure in an endemic area, and an elevated antibody response to *B. burgdorferi* (18). Unfortunately, serologic testing for Lyme disease is not standardized and both false-negative and more commonly false-positive results occur (20,21).

Recently, Steere et al. analyzed the diagnoses, serologic test results, and treatment results of patients evaluated in a Lyme disease clinic (22). Among the 788 patients studied, 180 (23%) had active Lyme disease, usually arthritis, encephalopathy, or polyneuropathy (22). An additional 156 (20%) had evidence of previous Lyme disease and another current illness, most commonly chronic fatigue syndrome (22). The remaining 452 patients (57%) did not have Lyme disease. Of the patients without Lyme disease, 45% had positive serologic test results for Lyme disease in other laboratories (22). The overwhelming reason for failure to respond to antibiotic therapy was incorrect diagnosis in 322 (79%) of 409 patients who had been treated before referral (22). Thus, misdiagnosis, particularly overdiagnosis, and unreliable serologic testing are major problems that clinicians and patients face in dealing with Lyme disease.

Treatment of Lyme disease is most successful when given early. Updated guidelines for treatment of Lyme disease have been recently published in 2000 (23). Treatment regimens are listed in Table 16.33. These guidelines from the Infectious Diseases Society of America suggest that for early Lyme disease, administration of doxycycline (100 mg twice daily) or amoxicillin (500 mg 3 times daily) for 14–21 days is the recommended treatment of early localized or early disseminated disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heartblock (23). Cefuroxime axetil (500 mg orally twice daily) should be reserved (because of higher cost) as an alternative agent for persons unable to take doxycycline or amoxicillin. Ceftriaxone (2g iv daily) is

effective but is not superior to oral agents for the treatment of Lyme disease in the absence of neurologic involvement or third-degree atrioventricular heart block; thus it is not recommended as a first line agent in this situation (23).

Recommendation	Dosage for adults
Preferred oral agent	
Amoxicillin	500 mg tid
Doxycycline	100 mg bid[b]
Alternative oral agent	
Cefuroxime axetil	500 mg bid
Preferred parenteral agent	
Ceftriaxone	2g iv once daily
Alternative parenteral agent	
Cefotaxime	2g iv tid
Penicillin G	18–24 million units iv/d divided into doses given q4h

[a]Infectious Diseases Society of American Guidelines
[b]Contraindicated in pregnancy

TABLE 16.33. RECOMMENDED ANTIMICROBIAL REGIMENS FOR TREATMENT OF PATIENTS WITH LYME DISEASE[a]

For early disease with acute neurological disease (e.g. meningitis or radiculopathy) ceftriaxone (2 g once daily) iv for 14–28 days) is recommended (23). Intravenous pencillin G 18–24 million units daily, divided into doses given every 4 hours is an acceptable alternative (23). In patients unable to tolerate penicillins and cephalosporins, doxycycline (200–400 mg/d) in 2 divided doses orally for 14–28 days is suggested; iv therapy with doxycycline is indicated in patients unable to take oral medication (23). Patients with third-degree atrioventricular heart block are treated similarly to those with neurologic manifestations except that hospitalization is recommended and a temporary pacemaker may be required (23). Other than doxycycline, which is contraindicated in pregnancy, the treatment of pregnant women is identical to that for non-pregnant patients.

Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally or intravenously (Table 16.33); doxycycline (100 mg twice daily orally) or amoxicillin (500 mg 3 times daily) for 28 days is recommended in patients without clinical manifestations of neurologic disease (23). Patients with arthritis and objective evidence of neurologic disease, the recommendation is iv ceftriaxone (2g once daily for 14–28 days) (23). Alternatives include iv cefotaxime (2g every 8 hours) or iv penicillin (18–24 million units daily) (23).

The role of primary antimicrobial prophylaxis to prevent Lyme disease after tick bites is controversial. Kaslow (24) suggested that the geographic variability in the proportion of ticks infected, the relatively long duration of tick attachment required for transmission, the low likelihood of significant symptomatic infection, and the availability of highly effective therapy for erythema migrans and other early stages of Lyme disease make routine prophylaxis for a tick bite unnecessary. Shapiro et al. (6) recently provided data to support this approach, in a prospective, randomized, placebo-controlled study. They found that the risk of Lyme disease in the placebo-treated patients was 1.2% (95% CI, 0.1–4.1%), which was not statistically

different from the risk in the amoxicillin-treated patients (0%; 95% CI, 0–1.5%). They concluded that even in an area in which Lyme disease is endemic, the risk of infection with *B. burgdorferi* after a recognized deer tick bite is so low that prophylactic antimicrobial treatment is not routinely indicated (6). On the other hand, Magid et al. (25), using a decision analysis approach, concluded that empiric treatment of patients with tick bites is indicated when the probability of *B. burgdorferi* infection after a bite is 0.036 or higher and may be preferred when the probability of infection ranges from 0.01 to 0.035. With a risk of infection less than 0.01, empiric therapy is not indicated. The IDSA guidelines suggest that routine prophylaxis is not indicated (23).

Presently, the major measures available for prevention of Lyme disease include wearing protective clothing in tick-infested areas during summer months, showering after exposure, and checking for attached ticks (10). Any ticks that are found must be removed. This is best accomplished by grasping the tick with forceps near the point of attachment and applying gentle traction. With the availability of a Lyme disease vaccine (LYMErix) another method of prevention is now available (26). this vaccine was approved by the FDA in 1998. Reported trials have demonstrated the efficacy of Lyme disease vaccine (27,28). The CDC estimates that the Lyme disease vcaccine is 76 % effective in preventing Lyme disease after three doses (26). See Chapter 25 for a detailed discussion of Lyme disease vaccine.

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Lyme Disease

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17

PREMATURE RUPTURE OF THE MEMBRANES

Premature rupture of the fetal membranes (PROM) is one of the most common problems in obstetrics, complicating approximately 5% to 10% of term pregnancies and up to 30% of preterm deliveries. Within the last 5 years, considerable progress has been made in aspects of our understanding and treatment of PROM. Although the etiology of PROM usually is not clinically evident in any given case, there is a considerable degree of consensus regarding management options. The problem is intricate; major variables influencing the outcome of a study are gestational age, date of the study, and population features. Variables affecting outcome include use of corticosteroids, tocolytics, and more potent antibiotics, and innovative approaches using various tests (such as amniocentesis, ultrasound, biophysical testing, and C-reactive maternal serum protein). Of major importance is the marked improvement in survival of low-birthweight infants.

DEFINITIONS

Nearly all recent publications are in agreement by defining PROM as rupture *at any time before the onset of contractions.* Unfortunately, “premature” also carries the connotation of preterm pregnancy. To avoid confusion, we use the word “preterm” to refer to gestational age less than 37 weeks.

The *latent period* is defined as the time from membrane rupture to onset of contractions. It is to be distinguished from a similar term, “latent phase,” which designates the early phase of labor before the active phase.

Respiratory distress syndrome (RDS) requires careful definition. Commonly used

criteria include early onset after birth; tachypnea, expiratory grunting, and retractions; cyanosis and hypoxia; and a chest radiograph showing a reticulogranular pattern with air bronchograms. Most studies use these criteria, but some use the term without defining RDS.

Various terms have been used recently to describe presumed *maternal* or *perinatal infections* related to PROM. During labor, designations have included “fever in labor,” “intrapartum fever,” “chorioamnionitis,” “amnionitis,” and “intrauterine infection.” The degree of temperature used to define “fever” is selected arbitrarily. The latter three terms usually are presumptive, based on combinations of maternal fever, uterine irritability or tenderness, leukocytosis, or purulent cervical discharge. After delivery, maternal infection is referred to as “endometritis” or “postpartum infection.” These diagnoses usually are based on fever, uterine tenderness, and exclusion of other sources of fever. In a few recent studies, presumed maternal infections were confirmed by reports of blood or genital tract cultures.

In neonates, the most common term used to report infection was *neonatal sepsis,* but this may mean strictly a positive blood culture or simply clinical signs or symptoms of sepsis. Neonatal meningitis and pneumonia also were noted in a few studies. Prophylactic administration of antibiotics to the mother, as in many reports, likely would influence detection of bacteremia in the newborn.

INCIDENCE

The incidence of PROM ranges from 5% to 10% of all deliveries, and preterm PROM occurs in approximately 1% of all pregnancies (1). Approximately 70% of cases of PROM occur in pregnancies at term, but more than 50% of cases in referral centers may occur in preterm pregnancies (2). Premature rupture of the membranes is the clinically recognized precipitating cause of about one third of all preterm births. Despite some progress in prolonging the latent period after preterm PROM and preventing recurrence (in women with bacterial vaginosis), preterm PROM remains a leading contributor to the overall problem of premature birth.

ETIOLOGY

In the vast majority of cases, the etiology is not clinically evident. Earlier studies had identified selected clinical conditions, such as cervical incompetence and polyhydramnios, as risk factors evident in some cases of PROM. In a large case-control study (341 cases of preterm PROM and 253 gestational age-matched controls), three factors were associated with preterm PROM in a multifactorial analysis (3). These three factors were previous preterm delivery (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.4–2.5), cigarette smoking (stopped during pregnancy: OR, 1.6; 95% CI, 0.8–3.3; continued during pregnancy: OR, 2.1; 95% CI, 1.4–3.1), and bleeding (first trimester: OR, 2.4; 95% CI, 1.5–3.9; third trimester: OR, 6.5; 95% CI, 1.9–23; more than one trimester: OR, 7.4; 95% CI, 2.2–26). This study enrolled controls at the same gestational age as cases (thus correcting for the decreasing frequency of coitus closer to term) and found no association between coitus and PROM. In a scholarly review of the etiology of preterm PROM, Parry and Strauss (4) identified numerous potential causes in any given case. These causes included a generalized decrease in tensile strength of membranes, local defects in the membranes, decreased amniotic fluid (AF) collagen, a change in collagen

structure, uterine irritability, apoptosis, collagen degradation, and membrane stretch. There is substantial evidence that subclinical infection may be a cause of PROM and not merely its result. In data from the Collaborative Perinatal Project (1959–1966), acute inflammation of the placental membranes was twice as common when membranes ruptured within 4 hours before labor than when the membranes ruptured after the onset of labor (5). Further evidence is provided by older bacteriologic studies showing associations between anaerobic isolates in endocervical cultures and PROM. More support for a role of infection is provided by studies showing an association between clinically diagnosed bacterial vaginosis (a condition with a shift in flora from lactobacilli to anaerobes, genital mycoplasmas, and *Gardnerella vaginalis*) and preterm birth/preterm PROM (see Chapter 19 for details.) Investigations into placental histology have provided correlates with clinical outcomes in cases of preterm PROM. Overall, in 235 cases, acute inflammation was seen in 43.4%, vascular lesions in 20.4%, inflammatory plus vascular lesions in 20.4%, normal findings in 13.2%, and “other” findings in 2.5% (Fig. 17.1).

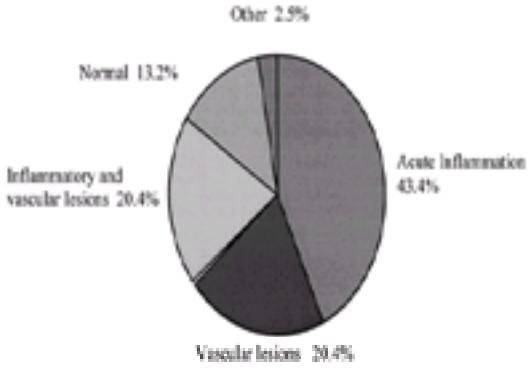


FIGURE 17.1. Placental histology in 235 cases of preterm premature rupture of the membranes. From ref. 6.

When acute inflammation was seen in the placenta (either by itself or mixed with vascular lesions), birth at less than 26 weeks was more common. Delivery for suspected or proved clinical infection also was more common (Fig. 17.2 and Fig. 17.3) (6). McGregor et al. (7) demonstrated that some genital bacteria elaborate enzymes such as proteases and collagenases that may act to weaken the membranes. Additional discussion of the relationship between infections and PROM is presented in Chapter 19.

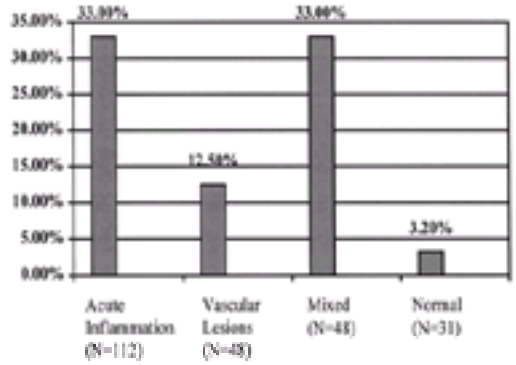


FIGURE 17.2. Outcome of premature rupture of the membranes by placental histology: percentage of births at less than 26 weeks. From ref. 6.

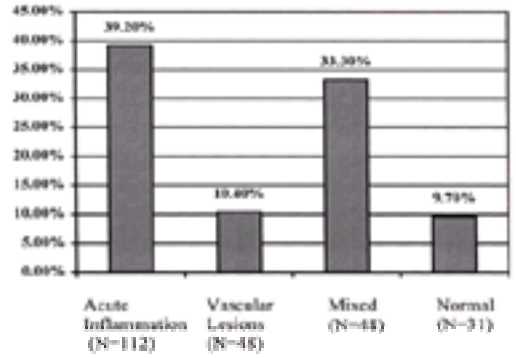


FIGURE 17.3. Outcome of premature rupture of the membranes by placental histology: delivery for infection. *Suspected or proved. From ref. 6.

DIAGNOSIS

In most instances, PROM is readily diagnosed by history, physical findings, and simple laboratory tests. Standard tests are based on determination of pH (Nitrazine test) or detection of a “ferning” pattern or fetal cells. Although these tests are accurate in approximately 95% of cases, each has well-known false-positive and false-negative results, especially in patients with small amounts of AF in the vagina. Other approaches to diagnosing PROM in such equivocal cases include biochemical and histochemical tests and intraamniotic injection of various dyes; however, these methods have not been widely used in practice.

Ultrasound examination has been used widely, because oligohydramnios suggests PROM, but there have been no evaluations of its sensitivity and specificity. In 1991, Lockwood and colleagues (8) observed that the presence of fetal fibronectin in the cervicovaginal secretions of second-trimester and third-trimester pregnant women identified a group at high risk for preterm delivery. The fibronectins are a family of

proteins found in plasma and extracellular matrix. Fetal fibronectin normally is found in AF and placental tissue (8). Eriksen et al. (9) reported a multicenter clinical trial comparing fetal fibronectin detection with standard tests for detection of ROM at term. There were 339 women with a clinical history of ROM and 67 controls. Fetal fibronectin showed excellent sensitivity (98.2%) but low specificity. The authors speculated that fetal fibronectin in cervicovaginal secretions may be a marker for impending labor, even without frank ROM.

CONSEQUENCES OF PREMATURE RUPTURE OF THE MEMBRANES

Onset Of Labor

At term, the onset of labor occurs within 24 hours after membrane rupture in 80% to 90% of patients (1). Among patients with PROM prior to term, longer latent periods occur. Latent periods of more than 24 hours occur in 57% to 83%, more than 72 hours in 15% to 26% (10), and 7 days or more in 19% to 41%. Johnson et al. (10) showed an inverse relationship between gestational age and the proportion of patients with latent periods longer than 3 days. For pregnancies between 25 and 32 weeks, 33% had latent periods longer than 3 days; for pregnancies of 33 to 34 weeks and 35 to 36 weeks, the corresponding values were 16% and 4.5%, respectively. Additional data on the natural history of preterm PROM (before 34 weeks) were provided by a population-based study at a hospital serving mainly indigent patients. (Data from referral institutions are skewed toward patients with longer latent periods; thus, a population-based study provides additional insight.) In 1988, Cox and colleagues (11) from Parkland Memorial Hospital in Dallas noted that 204 (76%) of 267 patients were already in labor at the time of admission. An additional 13 (5%) had an indicated delivery within a short time after admission, leaving only 50 patients (19%) as candidates for expectant management. Of these 50 patients, 30 (60%) went into spontaneous labor within less than 48 hours (11).

Effect Of Tocolytic Drugs

Two controlled trials have evaluated the use of tocolytic drugs in patients with PROM. Garite et al. (12) randomly assigned patients with PROM at 25 to 30 weeks' gestation to either expectant management or ritodrine tocolysis when labor developed. There were 39 patients in the tocolysis group and 40 in the expectant group. Corticosteroids were not used. Results are summarized in Table 17.1. Use of tocolytics showed no statistically significant or clinically meaningful benefit in increasing birthweight, gestational age, or time to delivery or in decreasing RDS. Of interest, there was a twofold increase in chorioamnionitis in the ritodrine group (p = 0.12), implicating labor as a potential sign of subclinical infection.

Outcome	Tocolysis (N = 39)	p	Expectancy (N = 40)
Birthweight (g)	1,387	NS	1,340
Gestational age (wk)	29.5	NS	28.9
Respiratory distress syndrome	51%	NS	58%
Chorioamnionitis	35%	0.12	18%
Time to delivery (days)	11.5[a]	NS	12.0
Neonatal stay (days)	47.5	0.08	57.0

[a]For group receiving tocolysis (N = 23), time was 6.1 days.
From Garite TJ, Keegan KA, Freeman RK, et al. A randomized of ritidine tocolysis versus expectant management in patients with premature rupture of membranes at 25 to 30 weeks of gestation. *Am J Obstet Gynecol* 1987;157:388.

TABLE 17.1. RITODRINE VERSUS EXPECTANCY IN PREMATURE RUPTURE OF THE MEMBRANE AT 25 TO 30 WEEKS' GESTATION

In 1988, Weiner and coworkers (13) reported a similarly designed study. Patients with PROM at 34 weeks' gestation were randomized to liberal use of tocolytics (usually ritodrine, when there were three or more contractions in an hour) or to expectancy. As in the study by Garite et al. (12), no corticosteroids were used. Magnesium sulfate was added to ritodrine as needed in the tocolytic group in an attempt to ablate contractions. Outcomes of this well-designed study are given in Table 17.2. No significant differences in overall outcome measures were seen. The authors observed prolongation of intrauterine time after the onset of contractions in the tocolytic group (105 ± 157 hours vs. 62 ± 72 hours; $p = 0.06$) and a significant increase in intrauterine time after onset of contractions for pregnancies of less than 28 weeks (232 ± 312 hours vs. 53 ± 87 hours; $p = 0.05$). However, there was no identifiable perinatal benefit accompanying these increases in intrauterine time, and there were no cost savings.

	Expectancy	Tocolysis
Birthweight (g)[a]	1518 ± 563	1648 ± 536
Umbilical vein pH[a]	7.35 ± 0.09	7.34 ± 0.08
Umbilical artery pH[a]	7.27 ± 0.09	7.25 ± 0.10
Sepsis (%)	3 (7.1)	3 (9.1)
Probable sepsis (%)	17 (40.5)	9 (27.3)
Respiratory distress syndrome (%)	22 (52.4)	15 (45.4)
Necrotizing enterocolitis (%)	10 (23.8)	6 (18.2)
Neonatal deaths (%)	5 (11.9)	3 (9.1)

[a]Data are given as mean ± SD. All differences are nonsignificant.
From Weiner CP, Renk K, Klugman M. The therapeutic efficacy and cost-effectiveness of aggressive tocolysis for premature labor associated with premature rupture of the membranes. *Am J Obstet Gynecol* 1988;159:216.

TABLE 17.2. NEONATAL OUTCOME IN A TRIAL OF TOCOLYTICS VERSUS EXPECTANCY WITH PREMATURE RUPTURE OF THE MEMBRANES £34 WEEKS

Earlier studies had shown a significant reduction in delivery at less than 24 hours when tocolytics were used, but these studies were small and had substantial design problems (14). In 1995, a comparison of short-term versus long-term tocolysis in preterm PROM at 26 to 35 weeks showed an adverse effect of “long-term tocolysis” (15). Patients with preterm PROM at 26 to 35 weeks were randomized to receive an intravenous b-mimetic drug either for less than 48 hours (n = 105) or until delivery (n = 136). All patients received corticosteroids, and group B streptococci (GBS) and gonococci were treated. There was no significant difference in the latent period or in neonatal infection, but there was a significant increase in both chorioamnionitis and endometritis with long-term tocolysis. Accordingly, use of tocolytics in patients with preterm PROM remains controversial, but the bulk of the evidence shows no benefit. If tocolytics are used, such as during transfer to a tertiary care center or possibly to obtain benefits of corticosteroids, we strongly believe that the course of tocolytics should be short term, i.e., limited to less than 48 hours.

COMPLICATIONS

The risks of PROM generally have been viewed as those of infection versus those of prematurity. Despite the limitations of using data from descriptive studies over a long period, it is clear that the most common complication among pregnancies with PROM before 37 weeks is RDS, which is found in 10% to 40% of neonates. *Bona fide* neonatal sepsis was documented in less than 10%, and amnionitis (based always on clinical criteria) occurred in approximately 3% to 31%. Endometritis developed in 0% to 29% in most groups, but it is not clear whether patients with amnionitis also were included in the endometritis category. Abruption after PROM has been reported in 4.0% to 6.3% of cases, which is higher than the usually quoted rate of 0.5% to 1.0% (16). Pulmonary hypoplasia is a serious fetal complication occurring in preterm PROM. Pulmonary hypoplasia is more common when there is very early preterm PROM, especially when it occurs in the presence of prolonged PROM with severe oligohydramnios. Vergani et al. (17) estimated a nearly 100% probability of lethal pulmonary hypoplasia when PROM occurred before 23 weeks and when there was severe oligohydramnios. With later gestational age at the onset of preterm PROM, the likelihood of pulmonary hypoplasia decreased. Notably, pulmonary hypoplasia was rare with preterm PROM more than 28 to 29 weeks, even with oligohydramnios. Kilbride and colleagues (18) provided a formula for predicting the probability of lethal pulmonary hypoplasia after mid-trimester PROM. When preterm PROM occurred at less than 25 weeks with severe oligohydramnios lasting more than14 days, the likelihood of lethal pulmonary hypoplasia was estimated to be 80%. At the other extreme, when preterm PROM occurred at more than 25 weeks and when there was either no severe oligohydramnios or severe oligohydramnios for less than 5 days, then the predicted probability of lethal pulmonary hypoplasia was only 2%. These data provide important information for counseling patients with mid-trimester PROM.

In 1991, the group at Irvine provided unique data on the recurrence risk for PROM. In a 5-year period, the recurrence rate was 32% (39/121) in patients who had PROM in an index pregnancy. Based on these data, the risk of recurrence is considerable, prompting patient education and close follow-up in subsequent pregnancies (19).

TREATMENT CONSIDERATIONS

The overall approach to management of PROM takes into consideration neonatal survival at the gestational age when rupture occurs. As shown in Figure 17.4, management usually is divided into four different phases of pregnancy. During the second trimester, neonatal survival is nil, leading numerous investigators to adopt a policy of expectant management. Early in the third trimester, neonatal survival rises markedly, but there is still considerable morbidity associated with delivery at this gestational age. In the mid third trimester, neonatal survival is high, but there is still attendant morbidity; in the late third trimester (at or near term), neonatal mortality and morbidity are low. In the sections that follow, neonatal outcome is one of the driving features in determining clinical management.

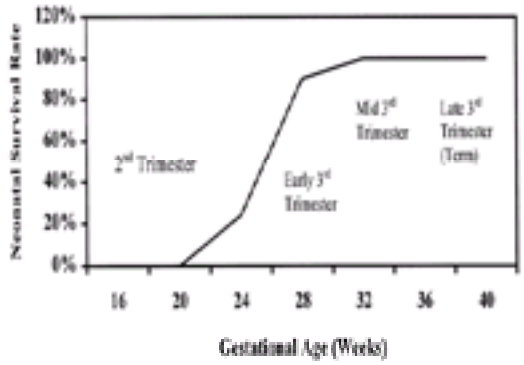


FIGURE 17.4. Management of premature rupture of the membranes by gestational age.

Preterm Premature Rupture of the Membranes

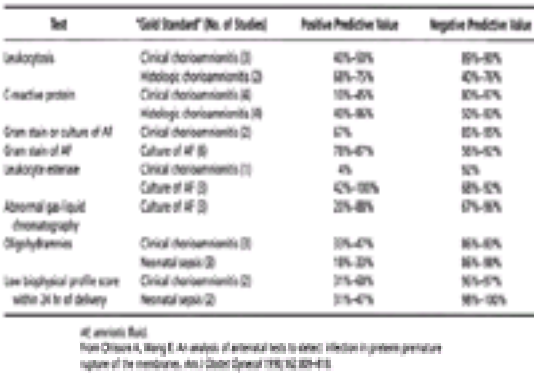
Infection

Diagnosis of Infection After Premature Rupture of the Membranes

Because of the great variation in risk of infection, attention has been directed at determining the infection risk of a given individual. Garite et al. (20) found that observing bacteria on a smear of AF (obtained by amniocentesis) was 78% specific and 81% sensitive for prediction of infection. However, AF was available in only half the patients, and amniocentesis may be accompanied by trauma, bleeding, initiation of labor, or introduction of infection. Romero and colleagues (21) compiled data indicating that, in the presence of preterm PROM, positive cultures of AF are obtained in 25% to 35% of patients.

Others have looked for less invasive predictors of infection (Table 17.3). The biophysical profile when performed every 48 hours has been reported to discriminate between cases at high and low risk for “infection” (22). Vintzeleos and colleagues

(22) reported that of 52 cases with a good score (8 or above), “infection” developed in only 6%. In comparison, of 16 cases with a low score (i.e., 7), “infection” was diagnosed in 15 (94%; $p < 0.01$). Ohlsson and Wang (23) reviewed the tests purporting to predict clinical maternal infection, histologic chorioamnionitis, positive cultures of AF, or neonatal sepsis after preterm PROM. As summarized in Table 17.3, these tests have widely varying predictive values. Because the prevalence of infection in either mother or neonate is never high, a high negative predictive value for a test is neither impressive nor especially useful clinically. Because none of these tests is ideal, they should be performed selectively and interpreted in the context of clinical findings.



Test	"Gold Standard" (No. of Studies)	Positive Predictive Value	Negative Predictive Value
Leukocytosis	Clinical chorioamnionitis (3)	40%–69%	89%–95%
	Histologic chorioamnionitis (2)	69%–75%	40%–76%
C-reactive protein	Clinical chorioamnionitis (4)	15%–85%	85%–97%
	Histologic chorioamnionitis (4)	40%–86%	50%–93%
Gram stain or culture of AF	Clinical chorioamnionitis (2)	67%	85%–95%
Gram stain of AF	Culture of AF (6)	78%–97%	50%–92%
Leukocyte esterase	Clinical chorioamnionitis (1)	4%	92%
	Culture of AF (3)	42%–100%	88%–92%
Abnormal gas/liquid chromatography	Culture of AF (3)	25%–88%	87%–98%
Oligohydramnios	Clinical chorioamnionitis (3)	33%–47%	86%–93%
	Neonatal sepsis (2)	18%–33%	86%–88%
Low biophysical profile score within 24 hr of delivery	Clinical chorioamnionitis (2)	31%–69%	90%–97%
	Neonatal sepsis (2)	31%–47%	98%–100%

AF, amniotic fluid.
From Ohlsson A, Wang E. An analysis of antenatal tests to detect infection in preterm premature rupture of the membranes. Am J Obstet Gynecol 1990; 162:809–818.

TABLE 17.3. PREDICTION OF INFECTION IN PREMATURE RUPTURE OF THE MEMBRANES

Effects of Steroids on Infection

There still is not complete agreement on the risks and benefits of steroids in preterm PROM. In the first metaanalysis in 1989, Ohlsson (24) included five randomized trials and concluded that the use of steroids “increases the incidence of endometritis and may increase neonatal infections.” In a 1990 metaanalysis, Crowley and coauthors (25) included seven trials in the assessment of maternal infection and five trials for neonatal infection. The odds ratios for maternal infection of 1.26 (95% CI, 0.6–2.4) and for neonatal infection of 1.6 (95% CI, 0.9–3.0) suggest that corticosteroid use is more likely to increase than to decrease infection after PROM, but the results are not statistically significant. The 1994 National Institutes of Health (NIH) Consensus Conference concluded that the risk of maternal and infant infection may be increased with corticosteroid use after PROM but that the magnitude of this risk was small. The recommendations are summarized in Box 1 (26).

Box 1

Corticosteroid Use in Preterm Premature Rupture of the Membranes: Recommendations from the 1994 NIH Consensus Conference

- Antenatal steroids in preterm PROM reduced the risk of RDS in randomized clinical trials, but the effect was less than with intact membranes.
- Strong evidence suggests reduced neonatal mortality and intraventricular hemorrhage with use in preterm PROM.
- “In fetuses <30–32 weeks...corticosteroid use is appropriate in the absence of chorioamnionitis.”

Effect of Latent Period and Vaginal Examination on Incidence of Amnionitis

In a number of earlier studies, the incidence of amnionitis rose with increasing length of the latent period (1), but other investigators found no increase in the incidence of amnionitis among preterm pregnancies with increasing latent periods. Lewis et al. (27) compared outcomes in women who had preterm PROM using either a digital examination (n = 127) or no digital examination (n = 144) prior to referral to their center. Although this was not a randomized comparison, the results are of great interest. Women with digital examination had a significantly shorter latent period (2.1 ± 4.0 days vs. 11.3 ± 13.4 days; $p < 0.001$), more maternal infection (44% vs. 33%; $p = 0.09$), and more positive AF cultures (11/25 [44%] vs. 10/63 [16%]; $p < 0.05$). Thus, routine vaginal examination should be avoided until labor develops in patients with preterm PROM.

Effect of Prophylactic Antibiotics

In patients with PROM prior to term, there are two rationales for prophylactic antibiotics. The first rationale is a clear one, namely, for prevention of perinatal GBS infection. Patients who have preterm PROM prior to 37 weeks are candidates for intrapartum GBS prophylaxis. Details of collection of cultures and timing of prophylaxis are given in Chapter 3. A second rationale for antibiotic prophylaxis is based on the hypothesis that either infection is the triggering cause of preterm PROM or infection ensuing after preterm PROM triggers the labor. Accordingly, the second rationale for prophylactic antibiotics has been to delay delivery after preterm PROM rather than to prevent clinically evident infection (see Chapter 19). We believe there is compelling evidence in favor of using broad-spectrum antibiotics in selected cases of preterm PROM. This support was provided in a metaanalysis (28) and in a prospective randomized trial (29). In the metaanalysis, 24 trials were identified and 13 were included, consisting of 1,594 women. However, only six of the trials were placebo controlled, and the trials were heterogeneous with regard to the antibiotics used. In addition, there was no standard use of steroids, tocolytics, or prophylaxis for GBS. Nevertheless, benefits were demonstrated in favor of women receiving antibiotics. The benefits included a significant delay in delivery within 7 days and reductions in chorioamnionitis and neonatal sepsis. There also were reductions in postpartum infection, neonatal death, neonatal pneumonia, and neonatal bacteremia,

but these differences were not statistically significant.

In 1997, Mercer and colleagues (29) reported the results of the large Maternal-Fetal Medicine Units Network Trial. In this study, patients were enrolled if they had preterm PROM for less than 72 hours at 24 to 32 weeks' gestation. Patients were excluded if there was chorioamnionitis, labor, or fetal distress. Patients were randomized to a course of ampicillin plus erythromycin (each for 2 days intravenously followed by up to 7 days orally) versus placebo. Patients with GBS were given treatment during the latent period and no tocolytics were used. At the time the study was designed, it was decided not to use corticosteroids in any patients. The primary endpoint was a prospectively defined composite of neonatal death, neonatal RDS, grade III or IV intraventricular hemorrhage, grade II or III necrotizing enterocolitis, or neonatal sepsis. As shown in Figure 17.5, patients randomized to antibiotic therapy had a significantly greater likelihood of remaining undelivered when assessed at 2, 7, 14, and 21 days. The primary composite outcome was significantly reduced in the total population and in the GBS-negative cohort. Individual adverse outcomes significantly reduced in the antibiotic group included RDS, chorioamnionitis, neonatal sepsis, and neonatal pneumonia. (Fig. 17.6 and Fig. 17.7). Table 17.4 summarizes the benefits of antibiotics in patients with preterm PROM and stratifies the results by total population versus the GBS-negative cohort. Subsequent to this trial, others studies have assessed the use of antibiotics in conjunction with antenatal corticosteroid therapy for patients with preterm PROM. Lovett and colleagues (30) assessed 112 women with PROM from 25 to 35 weeks and randomized them to ampicillin-sulbactam-amoxicillin clavulanate versus ampicillin-amoxicillin versus placebo. Tocolytics were used in this trial, and betamethasone was used weekly up to 32 weeks. Patients receiving the antibiotics had less serious neonatal complications, including neonatal death, RDS, and neonatal sepsis ($p < 0.05$). They also had significantly higher mean birthweight ($p = 0.03$). Lewis and colleagues (31) reported a randomized clinical trial of corticosteroids in patients with preterm PROM after treating the patients for a minimum of 12 hours with ampicillin-sulbactam. Antibiotics were continued for 7 days and steroids were repeated weekly. No tocolytics were used. The authors defined the primary outcome as the incidence of RDS; secondary outcome measures included latency and neonatal or maternal infections. In this study of 77 patients, no statistical significant difference in latency was noted comparing the steroid versus no steroid group, and both neonatal and maternal infections were similar. However, there was a significant reduction in the incidence of RDS: 18.4% in the steroid group compared with 43.6% in the no steroid group. The authors concluded that treating preterm PROM with a broad-spectrum antibiotic before corticosteroids decreased RDS without apparent adverse effect (31). In 1998, a metaanalysis of five trials on antibiotic and glucocorticoid treatment reportedly did not show a significant effect on outcomes, including maternal infection, neonatal sepsis, RDS, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal morbidity. In contrast, the authors noted “antibiotic therapy without concomitant use of glucocorticoids significantly reduced the odds of maternal infection, neonatal sepsis, and intraventricular hemorrhage substantially.” However, this metaanalysis did not include some of the more recent studies noted (32).

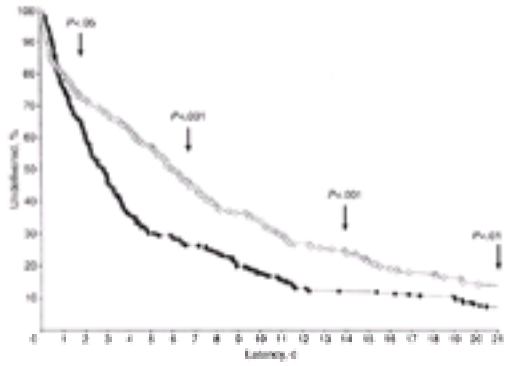


FIGURE 17.5. Prolongation of pregnancy in the group B streptococcus-negative cohort. Open circles, antibiotic group; solid circles, placebo. From ref. 29.

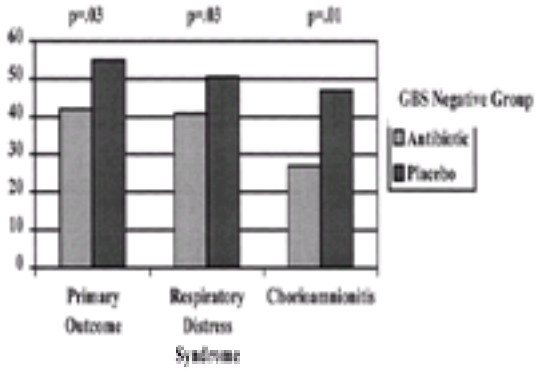


FIGURE 17.6. Selected outcomes in the Maternal-Fetal Medicine Units Network Trial. See text for definition of primary outcome. From ref. 29.

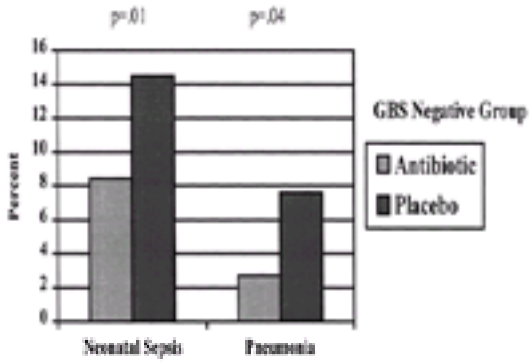


FIGURE 17.7. Additional outcomes in the Maternal-Fetal Medicine Units Network Trial. From ref. 29.

	Total Population	Group B Streptococcus-Negative Cohort
Primary outcome	↓ (p = 0.04)	↓ (p = 0.03)
Respiratory distress syndrome	↓ (p = 0.04)	↓ (p = 0.03)
Necrotizing enterocolitis	↓ (p = 0.03)	
Amnionitis	↓ (p = 0.01)	↓ (p = 0.01)
Neonatal sepsis		↓ (p = 0.01)
Neonatal pneumonia		↓ (p = 0.04)

From Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA 1997;278:989–995.

TABLE 17.4. MATERNAL-FETAL MEDICINE UNITS NETWORK TRIAL OF ANTIBIOTICS AFTER PRETERM PREMATURE RUPTURE OF THE MEMBRANES: SUMMARY OF BENEFITS

Widespread use of antibiotics in this situation has raised concern about selection pressure toward resistant organisms (33). However, in the Maternal-Fetal Medicine Units Network trial, there was no significant increase in maternal yeast infection or neonatal candidal sepsis, nor were there any cases of pseudomembranous colitis, maternal sepsis, or maternal death (29).

Respiratory Distress Syndrome

Effect of Steroids on Respiratory Distress Syndrome in Patients with Premature Rupture of the Membranes

The NIH Consensus Statement noted that the use of antenatal corticosteroids to reduce infant morbidity after PROM "remains controversial" (26). It also acknowledges that the magnitude of the reduction in RDS was not so great as with intact membranes and that steroid use may increase neonatal infection after PROM. However, as summarized in Box 1, corticosteroids are recommended to prevent RDS and other complications in selected cases of PROM.

Effect of Thyrotropin-Releasing Hormone on Respiratory Distress Syndrome in Patients with Premature Rupture of the Membranes

Thyrotropin-releasing hormone has been used in combination with antenatal steroids to accelerate fetal lung maturation. In two randomized trials, the combination of therapies led to few neonatal adverse effects and fewer cases with chronic lung problems (i.e., fewer days on the ventilator and less bronchopulmonary dysplasia). However, patients were not stratified by presence or absence of PROM. At present, use of thyrotropin-releasing hormone to accelerate lung maturity in the presence of PROM remains controversial (26).

Determination of Fetal Lung Maturity

Because RDS is the single greatest threat to infants with PROM, some investigators have determined the status of fetal pulmonary maturity and proceeded with delivery when there was lung maturity. Garite et al. (20) used amniocentesis and obtained fluid in about half of the cases. Others attempted to collect AF from the vagina and had success rates of 80% to 94% (34,35). Presence of either phosphatidylglycerol (PG) or a lecithin/sphingomyelin ratio more than two in AF collected vaginally has been reported to be a good predictor of pulmonary maturity (35).

In a larger series of patients with PROM before 36 weeks, Brame and McKenna (36) determined whether PG was present in the vaginal pool and delivered patients when there was presence of PG, spontaneous labor, or evidence of sepsis. Of 214 patients, 47 had PG present initially and were delivered. Of the remaining 167 patients, 36 (21%) developed PG and were induced or delivered by cesarean section. Evidence of maternal infection developed in 8 (5%), and spontaneous labor developed in 123 (74%) of the 167 patients. Phosphatidylglycerol in AF from the vagina reliably predicted fetal lung maturity. However, absence of PG did not necessarily mean that RDS would develop. Of the 131 patients who did not show PG in the vaginal pool in any sample, 82 (62%) were delivered of infants who had no RDS. Thus, even with PROM, delivery of a premature infant simply because its lungs showed biochemical maturity may be questioned in view of other potential hazards of prematurity and the difficulty of induction. Recently, some genital tract bacteria have been found to yield a false-positive test for PG.

Term Premature Rupture of the Membranes

In the last 5 years, new studies have influenced changes in the management of PROM at term. At the time of the last edition, induction of labor (with oxytocin) within 12 to 24 hours after PROM at term was a practice followed by most American obstetricians (37). Twenty-eight percent of obstetricians induced labor within 12 hours, and another 28% induced labor within 12 to 24 hours. Studies in the United States and Scandinavia supported the safety of this approach and reported shorter maternal hospital stays with less clinically evident neonatal infection (38,39). Induction of labor (with oxytocin) approximately 24 hours after PROM was a practice followed by approximately 8% of American obstetricians. An English report showed that induction of labor the morning after PROM at term (i.e., with latent periods up to 24 hours) was safe, with fewer cesarean deliveries than with immediate induction (40). Expectant management of PROM at term was a practice followed by only 7% (37). Although expectant management with inpatient observation had been shown to be safe in most patient populations (37,41,42), this approach has become less popular because of the inconvenience and expense of hospitalizations. Use of prostaglandin preparations to ripen the cervix and/or induce labor was a practice followed by approximately 32% of American obstetricians (37). Several studies have reported the safety and benefits of prostaglandins and have supported the increased popularity of induction with these preparations. In a large descriptive report, Meikle and coworkers (43), using vaginal prostaglandin E_2 (PGE_2) reported a low cesarean delivery rate (12%), infrequent hypertonicity, and low rates of maternal and neonatal infection (6.8% clinical chorioamnionitis and 0.6% neonatal bacteremia). All cases of infection developed in pregnancies with ROM longer than 24 hours. In a randomized

study, Mahmood et al. (44) compared vaginal PGE_2 gel with expectant management for 24 hours. Thereafter, oxytocin was used in both groups if the patient was not in labor. Use of PGE_2 was accompanied by shorter labor (20.1 vs. 26.9 hours; $p < 0.001$), less need for oxytocin (31% vs. 51%; $p < 0.001$), and no increase in maternal or neonatal infection (maternal, 12% vs. 15%, p = NS; neonatal, 4% in both groups). There was no difference in cesarean delivery rates (12% vs. 11%, respectively). In another randomized trial, Ray and coworkers (45) compared PGE_2 suppositories, placebo suppositories, and oxytocin. They also reported shorter labors, less maternal infection, and no difference in cesarean delivery rates with use of PGE_2 suppositories. In 1995, Chua and colleagues (46) reported a comparison of 3-mg PGE_2 pessaries versus placebo. On admission, patients had a single digital examination and were incorporated in the study if the Bishop score was less than 6. Oxytocin was given intravenously if there was no labor in 12 hours of if infection ensued. Patients in the prostaglandin group had significantly less likelihood of a need for oxytocin and a significantly shorter time to delivery. There was no significant difference in cesarean section rate, or in maternal or neonatal infection rates. In the largest trial of management of PROM at term, Hannah and colleagues (47) studied patients in a four-arm trial with approximately 1,250 patients in each arm. These four arms were as follows: expectant management plus oxytocin for induction as needed; induction with intravenous oxytocin shortly after admission; induction with PGE_2 gels in a dose of only 1 to 2 mg shortly after admission; and expectant management followed by PGE_2 induction as needed. One methodologic concern regarding this study is the low dose of PGE_2 gel used vaginally. With most patients receiving less than 2 mg, the dose was smaller than the dose used in most American trials. As shown in Figure 17.8, patients randomized to expectant management initially had significantly longer times to delivery than patients randomized to either of the induction arms ($p < 0.001$). In addition, the rate of clinically diagnosed chorioamnionitis was less in the patients randomized to induction initially (with significance achieved at $p < 0.01$ comparing arm 1 vs. arm 2). The distribution of postpartum infection was similar to that of chorioamnionitis. In addition, there was no significant difference in rates of neonatal infection or cesarean section. Of note, patient satisfaction was significantly higher in the induction arms.

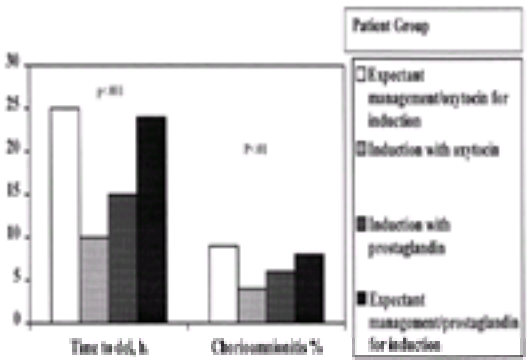


FIGURE 17.8. Selected outcomes in the international term premature upture of the membranes trial. From ref. 47.

In 1997, a large metaanalysis of 23 studies that included nearly 7,500 patients concluded that conservative management may result in more maternal infections than immediate induction with either oxytocin or prostaglandins (48). This metaanalysis also showed that the rate of chorioamnionitis was higher in patients induced with prostaglandin versus those induced with oxytocin. However, this metaanalysis was heavily influenced by the large international trial (47), and, as noted earlier, this trial used a very low dose of prostaglandin. Within the last few years, intravaginal misoprostol (a PGE_1 analog) has assumed marked popularity for induction because of its efficacy and low cost. In 1997, a comparison of intravaginal misoprostol (50 µg every 4 hours for a maximum of 12 tablets) was compared with oxytocin in women with single pregnancies and an unfavorable cervix (<2 cm dilated and <80% effaced) (49). The results of this trial are given in Table 17.5. Overall, patients randomized to misoprostol had a shorter induction time by approximately 2 hours, but they had significantly more uterine tachysystole. Of note, over 85% of patients required only one dose of misoprostol. Compared to other trials evaluating misoprostol in patients at term with intact membranes, the dose used in this trial is relatively high.

	Misoprostol (N = 70)	P	Oxytocin (N = 71)
Induction time (min)	416.0	0.04	539
One dose (%)	85.7		
Uterine tachysystole (%)*	28.6	<0.04	14.0

*≥5 contractions/10 min × 20 min.
No difference in mode of delivery or any other complications.
From Sanchez-Ramos L, Olsen AH, Kaunitz AM, et al. Labor induction with intravaginal misoprostol in term premature rupture of membranes: a randomized study. Obstet Gynecol 1997;89:909-912.

TABLE 17.5. MISOPROSTOL VERSUS OXYTOCIN IN PRETERM PREMATURE RUPTURE OF THE MEMBRANES

In summary, a considerable amount of evidence supports the safety and efficacy of induction with prostaglandin preparations for pregnancies with PROM at or near term. These trials support the wide popularity of these techniques.

MATERNAL MORTALITY

Among studies, there was mention of only one death among more than 3,000 women with PROM. This patient died of chorioamnionitis, severe toxemia, and cardiorespiratory arrest at 29 weeks' gestation. Rupture of the membranes and signs of chorioamnionitis were not recognized. From the same institution, there are reports from the early 1950s of four other maternal deaths from long-standing infection (10). Other citations of maternal death from sepsis complicating PROM appear

sporadically.

MANAGEMENT OPTIONS

As shown in Table 17.6, options for management vary by gestational age at the time of PROM.

Gestational Age	Option	Controversial
<24 wk	Induction vs expectancy; antibiotics for GBS	
24–32 wk	Expectancy; antibiotics for GBS; ? tocolytics for 48 hr; antibiotics to prolong latent period; fetal testing	Thyrotropin-releasing hormone
33–35 wk	Expectancy vs induction, especially if "mature"	
At or near term (≥35 wk)	Early induction (6–24 hr); late induction; prostaglandin induction; expectancy; GBS prophylaxis per CDC/ACOG guideline	

CDC/ACOG, Centers for Disease Control and Prevention/American College of Obstetricians and Gynecologists; GBS, group B streptococcus.

TABLE 17.6. SUMMARY OF MANAGEMENT OPTIONS

Premature Rupture of the Membranes at Less than 25 Weeks

For PROM before viability (approximately £24 weeks), several descriptive reports have demonstrated a highly variable latent period, high maternal infection rates (but with little serious morbidity), and an appreciable survival rate, especially when delivery occurs after week 24 (Table 17.7). Recent outcome data with expectant management of PROM in the second trimester showed perinatal survival and “intact” neurologic survival stratified by the gestational age at the time of PROM (Fig. 17.9) (50). In summary, when gestational age occurred from weeks 14 to 19, overall survival was only 40%; when PROM occurred at 20 to 25 weeks, overall survival was nearly 90%. The alternative to expectant management is induction. In the patient with PROM this early in pregnancy, we individualize the decision and involve the family fully. In the proper setting, we offer expectant management.

Outcome Measure	Result
Gestational age at rupture of the membranes [median (range)]	23.5 wk (17–26)
Latent period [median (range)]	7.6 days (1–161)
Amnionitis [mean (range)]	39% (22%–63%)
Survival [mean (range)]	38% (25%–46%)
Normal development at 1 yr [mean (range)]	59% (20%–68%)

Data from references 51 to 58.

TABLE 17.7. PREMATURE RUPTURE OF THE MEMBRANES AT £24 WEEKS

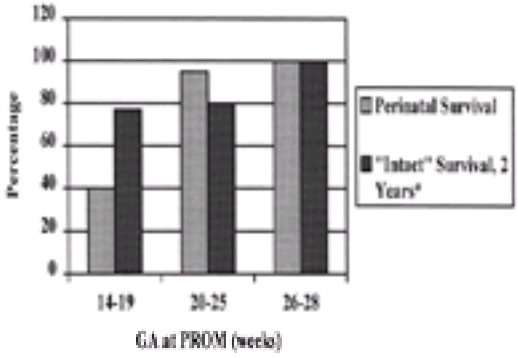


FIGURE 17.9. Outcome with expected management of second-trimester premature rupture of the membranes. *Survival at 2 years without major impairment. From ref. 50.

Premature Rupture of the Membranes at 25 to 32 Weeks

For management of PROM after viability but before 32 weeks, our practice is to generally follow expectant management and proceed with delivery where there is spontaneous onset of labor or clinical evidence of infection. We follow national guidelines for intrapartum prophylaxis for prevention of GBS neonatal sepsis. For patients in whom delivery is not imminent, we also obtain an appropriate culture for GBS from the rectovaginal area. We administer corticosteroids in a standard regimen. We also apply broad-spectrum antibiotic therapy, usually following the ampicillin-amoxicillin plus erythromycin regimen of the Maternal-Fetal Medicine Units Network Trial (29). This regimen is limited to 7 days. When the patient goes into labor, we begin GBS prophylaxis as recommended by the Centers for Disease Control and Prevention (CDC). At the University of Colorado, we do not use tocolytics during this gestational age in patients with preterm PROM.

Premature Rupture of the Membranes at 33 to 36 Weeks

When there is evidence of fetal lung maturity, two trials have reported benefits to induction versus continued expectancy. In 1993, Mercer and coworkers (59) compared induction (n = 46) with continued expectancy (n = 47) in pregnancies at 32 to 36 weeks with evidence of fetal lung maturity. Induction had several benefits, including a shorter time to delivery (14 vs. 36 hours; $p < 0.001$), shorter maternal hospital stay (2.3 vs. 3.5 days; $p < 0.001$), and less chorioamnionitis (11% vs. 28%; $p = 0.06$). Neonatal hospital stay also was shorter (6.3 vs. 7.3 days), but this difference was not significant. Although the authors found less clinically diagnosed neonatal sepsis in the induction group (28% vs. 60%; $p < 0.003$), there was no

difference in confirmed sepsis (seven cases in the induction group vs. four in the expectant group). There were no significant differences in the rates of cesarean delivery, postpartum infection, or neonatal survival. Spinnato et al. (60) also found advantages to induction versus expectancy. Despite the reasons advanced by these authors, there is no compelling reason to induce all pregnancies with PROM simply because there is evidence of lung maturity. There is no improvement in Perinatal mortality (PNM), and in other populations, induction in the presence of an unripe cervix at 32 to 36 weeks might result in higher rates of infection or cesarean delivery.

For pregnancies with PROM at 33 to 35 weeks, we generally use expectant management. We do not routinely perform amniocentesis, but use it selectively when we suspect infection or growth restriction. We assess fetal status during expectant management with usual testing, mainly daily NSTs with biophysical profiles as needed for backup. In selected pregnancies at 33 to 35 weeks, we induce labor in the presence of lung maturity. Such situations include development of a favorable cervix (noted on a speculum examination) or poor patient compliance. We proceed with delivery when there are maternal or fetal indications including evidence of infection. For pregnancies with PROM at 33 to 35 weeks, we give intrapartum prophylaxis per the CDC/ACOG (American College of Obstetricians and Gynecologists) guidelines. We also obtain an appropriate rectovaginal culture for GBS at the time of admission, unless delivery is imminent. We then begin empiric intravenous prophylaxis until the culture result is available and is negative. If the culture is positive at 33 to 35 weeks, we continue intravenous penicillin for 48 hours, then stop and reculture.

Premature Rupture of the Membranes at or Near Term (35 Weeks or More)

With the advent of effective and safe prostaglandin preparations, we have used these preparations preferentially. In selected circumstances, such as a ripe cervix or where we suspect uteroplacental insufficiency, we will use oxytocin preferentially. Until several years ago, our preferred preparation was vaginal PGE_2 gels. More recently we have used misoprostol. Group B streptococcus prophylaxis for patients at or near term is used consistent with CDC/ACOG guidelines. Thus, intrapartum prophylaxis for prevention of GBS infection is used in patients at less than 37 weeks, in those with a previously affected child, in those with GBS bacteriuria in this pregnancy, in those with greater than 18 hours ROM, or in those patients who had a positive genital culture at 5 to 37 weeks.

These are largely empiric approaches, summarized in Box 2,Box 3,Box 4 and Box 5. It is certain that a scientifically sound basis for the management of PROM hinges on a much more thorough understanding of its pathophysiology. Indeed, that understanding holds the prospect of not only improved management after PROM, but ultimately strategies for its prevention.

Box 2

Summary of Management: PROM <24 Weeks

- Induction versus expectancy, depending on gestational age and patient desires
- No data on steroids, tocolytics, or antibiotics (for GBS prophylaxis or prolonging pregnancy)

Box 3

Summary of Management: PROM at 25–32 Weeks

- Expectancy
- GBS prophylaxis
- Corticosteroids
- Antibiotics for 7 days (ampicillin + erythromycin *or* clindamycin) or alternative regimens
- ??Tocolytics for 48 hours

Box 4

Summary of Management: PROM at 33–35 Weeks

- Expectancy versus induction, especially if “mature”
- GBS prophylaxis

Box 5

Summary of Management: PROM At or Near Term

- Induction usually preferred, with oxytocin or prostaglandin preparations (especially with unripe cervix)
- GBS prophylaxis with ROM >12–18 hours

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18

INTRAAMNIOTIC INFECTION

In the last 5 years, exciting new information regarding intraamniotic infection (IAI) has developed. There is gathering evidence that intrauterine exposure to bacteria may be the cause of important neonatal adverse outcomes, including cerebral palsy and respiratory distress syndrome (RDS). In addition, several strategies for the prevention of IAI have been recognized. It previously had been stated that clinically evident intrauterine infection occurred in approximately 1% of pregnancies. Prospective studies published in the last few years report rates of 4% to 10% among public and private patients (1,2 and 3).

Clinicians continue to apply a number of terms to this entity, including chorioamnionitis, amnionitis, intrapartum infection, amniotic fluid (AF) infection, and IAI. We use the last designation to distinguish this clinical syndrome from bacterial colonization of AF and from histologic inflammation of the cord or placenta. However, where authors have used alternate expressions, we follow their terminology.

It is possible that subclinical infection of the uterine cavity and AF may lead to substantial adverse pregnancy effects, such as premature labor and premature rupture of the membranes (PROM). These developments are discussed in Chapter 19.

PATHOGENESIS

Prior to labor and rupture of the membranes (ROM), the amniotic cavity nearly always is sterile. The physical and chemical barriers formed by the intact placental membranes and cervical mucus usually are effective in preventing entry of bacteria. With the onset of labor or with ROM, bacteria from the lower genital tract commonly ascend into the amniotic cavity. In some patients, the numbers of bacteria increase

with the interval after ROM. This ascending route is the most common pathway for development of IAI (4). A hematogenous or transplacental route of infection occurs with *Listeria monocytogenes* (5,6 and 7). Amniotic infection with this aerobic Gram-positive rod may result in fetal demise. Other virulent organisms, such as group A streptococci, may lead to a similar bloodborne infection (8).

Intraamniotic infection has been reported in 1% to 18% of women after a cervical cerclage, especially when there is advanced dilation (9,10 and 11). In a report by Charles and Edwards (9), 11 (9.6%) of 115 patients developed chorioamnionitis within 4 weeks of placing a cervical cerclage, and another 17 (14.8%) developed infection 4 weeks or more after this surgical procedure (9). Mitra et al. (11) reported 40 cases in which emergency McDonald cerclage was performed in the presence of cervical dilation (<1 cm) and effacement (>50%) with membranes visible at the external os. They noted chorioamnionitis in 2 (5%) cases, even though antibiotics had been used in about half of the patients.

Intraamniotic infection may occur as a complication of invasive diagnostic procedures, such as amniocentesis, intrauterine transfusion, chorionic villus sampling, and percutaneous umbilical blood sampling. With diagnostic amniocentesis, amnionitis has been reported in 0% to 1% of cases (12). With intrauterine transfusion, infection is reported to develop in approximately 10%. Chorioamnionitis is a rare complication of chorionic villus sampling. Although IAI is very rare after percutaneous umbilical blood sampling and the fetal loss rate accompanying this procedure is 1% to 2%, infection is responsible for a high percentage of losses and may lead to life-threatening maternal complications (13).

Risk factors for IAI have been identified. Coitus does not appear to be a risk factor for clinical chorioamnionitis, histologic chorioamnionitis, PROM, or preterm birth (14,15 and 16). Most cases occur in 90% of deliveries at term, and risk factors are mainly those of complicated or prolonged labor. In two large investigations using logistic regression analysis, the following risk factors were identified: low parity, prolonged duration of membrane rupture, prolonged duration of labor, larger number of vaginal examinations, and duration of internal fetal monitoring (1,2,17,18). Other data from a randomized trial of active management of labor showed that chorioamnionitis occurs less frequently when labor management features early diagnosis of abnormalities and early intervention (3). We believe internal fetal monitoring should be used if it enables practitioners to diagnose and treat such abnormalities more efficiently.

Microbiology

Intraamniotic infection is polymicrobial, involving both aerobic and anaerobic bacteria. In a controlled study, Gibbs and colleagues (19) collected AF via an intrauterine pressure catheter from patients with fever and clinical IAI and from asymptomatic matched control patients in labor. In the AF of patients with IAI, the following high-virulence organisms were found: *Bacteroides* sp, 25%; group B streptococci (GBS), 12%; other aerobic streptococci, 13%; *Escherichia coli,* 10%; other aerobic Gram-negative rods, 10%; *Clostridium* sp, 9%; *Peptococcus* sp, 7%; and *Fusobacterium* sp, 6%. A mean of 2.2 isolates was recovered from the AF of these patients. Of the 52 patients with clinical IAI, 48% had aerobes and anaerobes isolated; 38% had aerobes only; 8% had anaerobes alone; and 6% had no aerobic or anaerobic bacteria in the AF. The rate of isolation of these high-virulence isolates

from AF was lower in 52 matched uninfected patients. Twenty-three percent of the control patients had high-virulence isolates, but only 7.7% had these isolates at a concentration greater than 10^2 colony-forming units per milliliter (CFU/mL). In comparison, 69% of patients with IAI had greater than 10^2 CFU of a high-virulence organism per milliliter of AF. Table 18.1 shows the number of patients in each group with high-virulence and low-virulence bacteria and quantitation of the isolates. The study concluded that the AF cultures from patients with IAI were more likely to have 10^2 CFU/mL of any isolate, any number of high-virulence isolates, and more than 10^2 CFU/mL of a high-virulence isolate. The isolation of low-virulence organisms, such as lactobacilli, diphtheroids, and *Staphylococcus epidermidis,* was similar in both the IAI and control groups. Table 18.2 shows the most common AF isolates found in over 400 cases of IAI.

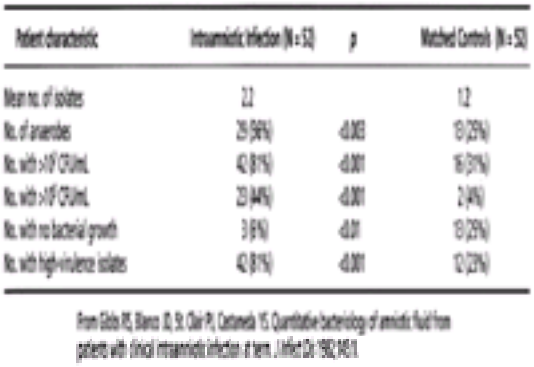


TABLE 18.1. CHARACTERISTICS OF AMNIOTIC FLUID FROM PATIENTS WITH INTRAAMNIOTIC INFECTION AND FROM CONTROLS

Organism[a]	No. (%)
Group B streptococci	59 (14.6)
Escherichia coli	33 (8.2)
Enterococci	22 (5.4)
Gardnerella vaginalis	99 (24.5)
Peptostreptococci	38 (9.4)
Bacteroides bivius	119 (29.4)
Bacteroides fragilis	14 (3.4)
Fusobacterium sp	22 (5.4)
Mycoplasma hominis	123 (30.4)
Ureaplasma urealyticum	190 (47.0)

[a]For bacteria, all isolates shown were found in concentrations > 10^2 CFU/mL. Genital mycoplasmas were cultured qualitatively.
From Sperling RS, Newton E, Gibbs RS. Intraaminiotic infection in low-birth-weight infants. *J Infect Dis* 1988;157:113.

TABLE 18.2. AMNIOTIC FLUID ISOLATES IN 404 CASES OF INTRAAMNIOTIC INFECTION

Even though GBS and *E. coli* were isolated with modest frequency (15% and 8%, respectively), they are strongly associated with either maternal or neonatal

bacteremia. When GBS was found in the AF of women with IAI, maternal or neonatal bacteremia was detected in 25% (15 of 60) of cases. When *E. coli* was found, maternal or neonatal bacteremia was detected in 33% (11/33). These rates of bacteremia are significantly higher ($p < 0.05$) than the 10% rate for all organisms and the 1% rate for anaerobes (18). Even though *Gardnerella vaginalis* was isolated with high frequency, its pathogenic role has remained unclear. In a case-control study, *G. vaginalis* was isolated with similar frequencies in IAI and control cases (24/86 [28%] vs. 18/86 [21%], respectively; p = NS), and there was no detectable maternal antibody response to this organism (21).

Other microbiologic studies have reported similar isolates (9,22). On rare occasions, *Neisseria gonorrhoeae* may cause amnionitis (23). In a controlled study of IAI, Blanco and coworkers (24) reported that 35% of AF from 52 patients with IAI yielded *Mycoplasma hominis,* whereas only 8% of AF from 52 matched controls had *M. hominis* ($p < 0.001$). Of the 18 AFs positive for *M. hominis,* 15 also contained fewer than 10^2 CFU/mL of a high-virulence bacterial isolate. *Ureaplasma urealyticum* was isolated from the AF from 50% of the infected and uninfected patients. Thus, *M. hominis* is present more commonly in the AF of infected patients but usually in association with other bacteria of known virulence. Furthermore, the patients with IAI and *M. hominis* in the AF responded to antibiotic therapy not specific for this organism; in the control patients, *M. hominis* was isolated from AF on occasion without apparent sequelae. In a subsequent study, Gibbs and colleagues (25) found *M. hominis* in the blood of 2% of women with IAI and with *M. hominis* in the AF. This rate of serologic response was significantly greater than that in asymptomatic control women or infected women without IAI in the AF ($p < 0.001$) (25). Blood cultures and serologic results did not clarify the role of *U. urealyticum.* Therefore, the pathogenic potential of *M. hominis* is high, but the pathogenic status of *U. urealyticum* in IAI is unclear.

At present, evidence for the role of *Chlamydia trachomatis* in AF infections is unconvincing. Wager et al. (26) showed that the rate of intrapartum fever was higher in patients with antepartum *C. trachomatis* infection (9%) than in patients without *C. trachomatis* isolated from the cervix (1%). The data must be interpreted cautiously because of the limited numbers and because the control group may not have been similar. No significant differences in seroprevalence or serologic changes in antichlamydial antibodies (immunoglobulins G [IgG] and M [IgM]) were apparent between IAI and uninfected groups (27).

Pregnant women appear to be especially susceptible to infection with *L. monocytogenes,* an organism that has caused regular outbreaks of infection often associated with contaminated dairy products. Maternal sepsis may occur, and fetal infection may cause demise *in utero.*

Several investigational approaches have revealed a strong association between bacterial vaginosis (BV) and clinical as well as histologic chorioamnionitis (28). First, predominant organisms involved in IAI (i.e., anaerobes and mycoplasmas plus *G. vaginalis*) are the organisms found in vaginal cultures of women with BV. Second, strong associations were found among these organisms in the AF of women with IAI; when one of these organisms was found, the others were significantly more likely to be present ($p < 0.001$). Third, among at-risk women in labor, there was a significant association between a diagnosis of IAI and finding BV by Gram stain. Of women with BV, 69% (22/32) of this high-risk group had IAI, whereas of women without BV, 46%

(43/93) had IAI (p = 0.05). Finally, there is a significant relationship between prenatal infection with BV and subsequent development of AF infection. Among 534 women in the second or third trimester, BV was present in 19%. Even though women with and without BV were similar with regard to several risk factors, AF infection occurred more often in the women with BV (9% vs. 4%; $p < 0.05$). These data suggest that antepartum treatment of BV might decrease the development of IAI, but in a randomized treatment trial of women with BV during pregnancy, the incidence of clinical amnionitis was similar in the group treated with clindamycin cream and in the group treated with placebo cream (5.9% vs. 6.3%; p = NS) (29). Similarly, prenatal treatment of asymptomatic BV did not result in a reduction in IAI (30). In the several treatment trials of BV in pregnancy with oral regimens, the effect of treatment on IAI has not been reported. Bacterial vaginosis in pregnancy should be treated in asymptomatic women and in women at high risk for preterm birth, such as women with previous preterm birth or preterm PROM. Currently, it is not standard practice to screen and treat all pregnant women who have BV (see also Chapter 12).

Host Defense Mechanisms

Although in most pregnant patients bacteria gain access to the amniotic cavity after ROM, few patients develop IAI. Possible defense mechanisms described are polymorphonuclear leukocytes, lysozyme, b-lysine, transferrin, immunoglobulins, and inhibitory factors. Polymorphonuclear leukocytes commonly appear in the AF of laboring women following ROM at or near term. Although their presence is associated with fever in labor, many women without symptoms have white cells in the AF, and fulminant amnionitis such as that caused by GBS may not lead to leukocytes in the AF. Among women with preterm labor with intact membranes, the AF white blood cell count (>50/mm^3) had the following diagnostic indices for the detection of a positive AF culture: sensitivity, 64%; specificity, 94%; positive predictive value, 54%; and negative predictive value, 96%, in a population with a prevalence of positive cultures of 9.2% (11/120) (31). Several groups have shown that AF appears to inhibit bacterial growth (32), but neither a specific inhibitor nor its clinical significance has been demonstrated satisfactorily (33,34).

Immunoglobulins are found in low but measurable levels in AF. The mean level of IgG in the AF from patients with IAI is significantly higher than the mean level in control patients (34), but these levels are still well below levels found in normal sera. Furthermore, the higher mean IgG level in IAI fluids may be a result of nonspecific exudation of serum proteins, including IgG, into AF. Accordingly, these IgGs may not be specific for the infecting organism and may have no role in the infection.

Sequelae

Once IAI develops, the fetus may swallow and aspirate the infected fluid. The fetus is prone to develop pneumonia, enteritis, meningitis, and sepsis, as the fetal immunologic system may not be fully developed. Indeed, clinical diagnosis of chorioamnionitis is one of the most important risk factors for neonatal sepsis. Yancy and colleagues (35) reported an odds ratio for the development of neonatal sepsis of 25 for chorioamnionitis compared with an odds ratio of less than 5 for preterm delivery, rupture of membranes greater than 12 hours, endometritis, and GBS colonization. In the mother, endomyometritis, peritonitis, and sepsis may develop as the infection spreads outward from the amniotic cavity.

DIAGNOSIS

Diagnosis of clinical IAI requires a high index of suspicion because the clinical criteria are neither specific nor sensitive (36). Moreover, usual laboratory indicators of infection, such as positive stains for organisms or leukocytes and positive cultures, are found much more frequently than clinically evident infection is diagnosed.

Clinical Criteria in the Mother and Fetus

The clinical diagnosis usually is based on fever, maternal or fetal tachycardia, uterine tenderness, foul odor of the AF, and leukocytosis (36,37 and 38). Other causes of fever in the parturient include infection of the urinary tract or other organ systems. The differential diagnosis of fetal tachycardia consists of prematurity, medications, arrhythmia, and perhaps hypoxia; other possible causes for maternal tachycardia are drugs, hypotension, dehydration, and anxiety.

In general, the most common clinical criteria are fever, leukocytosis, and ruptured membranes; fetal and maternal tachycardia are noted in variable percentages of cases. Foul AF and uterine tenderness, although more specific signs, occur in a minority of cases. In cases of clinical chorioamnionitis, maternal fever was present in 85% to 99%, fetal tachycardia in 37% to 82%, maternal tachycardia in 19% to 37%, uterine tenderness in 13% to 16%, and foul AF in 9% to 22% (4,39).

Laboratory Criteria in the Mother

To support a clinical suspicion of chorioamnionitis, the physician commonly turns to laboratory tests for assistance. A urine specimen should be obtained for analysis. A high specific gravity may suggest dehydration, and, in a properly collected specimen, bacteriuria and pyuria suggest urinary tract infection. A portion of the urine specimen should be sent for culture and sensitivity testing. In patients with fever, two sets of blood cultures should be drawn, but bacteremia occurs in only about 10%. Because peripheral blood leukocytosis occurs commonly in normal labor, we must not rely solely upon this result to suggest infection.

Direct examination of the AF may provide important diagnostic information (Fig. 18.1). We have found that samples can be collected by aspiration of an intrauterine pressure catheter in more than 50% of cases with fever in labor. Alternative routes include needle aspiration of the forewaters or amniocentesis. When the specimen is collected by aspiration of either a catheter or the forewaters, contamination is possible. Thus, when aspirating a catheter, discard the first 5 to 7 mL of fluid. With any technique, it is helpful to perform a Gram stain and plate the specimen promptly and quantitatively to help distinguish mere contaminants from bacteria causing infection.

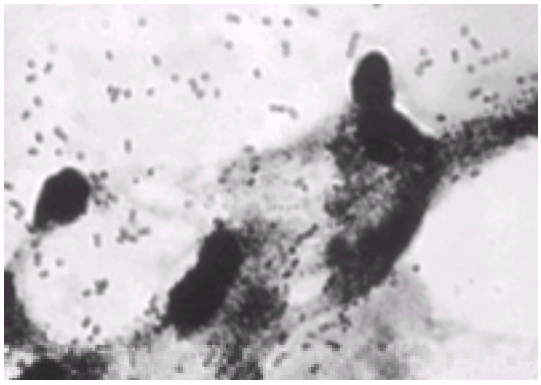


FIGURE 18.1. Gram stain of amniotic fluid from a patient with clinical intraamniotic infection due to group B streptococci. Note numerous Gram-positive cocci.

In studies of patients with clinical signs of infection, investigators have found a significant association between observing bacteria in a stain of uncentrifuged AF on the one hand and colony counts greater than 10^2 or 10^3/mL and clinical infection on the other (19,21). However, in specimens from asymptomatic patients who are in labor with ruptured membranes, bacteria may be seen very commonly. Yet, few of these patients developed clinical infection (40). Accordingly, in patients with suspected IAI, observing bacteria on a smear of uncentrifuged fluid supports the diagnosis, but there may be either false-positive or false-negative results.

In a case-control study of 42 patients, leukocyte esterase was evaluated as a predictor. Leukocyte esterase activity was detected by placing a Chemstrip 9 dipstick in the sample of AF for 1 second. The result was read from a color chart in 1 minute. Results in this pilot study were excellent (sensitivity, 91%; specificity, 95%) but need to be confirmed in larger studies (41). Subsequently, in a series of 57 AFs (18 from infected pregnancies), the dipstick assay again was excellent (sensitivity, 94%; specificity, 95%; positive predictive value, 97%; and negative predictive value, 90%), but a new spectrophotometric assay was reported to be even better (sensitivity and specificity, 100%) (42).

Determination of amniotic glucose concentration is a practical test for diagnosing clinical chorioamnionitis. A low value (<5 mg/dL) correlates with both clinical evidence of chorioamnionitis and a positive AF culture (31,43). With an amniotic glucose concentration less than 5 mg/dL, the likelihood of positive AF culture is approximately 90%. On the other hand, when the AF glucose concentration is greater than 20 mg/dL, then the likelihood of a positive culture is approximately 2%. At intermediate values (i.e., 14 to 15 mg/dL), the likelihood of a positive amniotic culture is 30% to 50%.

Clinical Criteria in the Neonate

Most cases of early-onset neonatal sepsis originate *in utero.* Immediately after delivery, the diagnosis of septicemia is difficult because the neonate's response to infection is impaired, and the reaction often is nonspecific. The earliest signs are

subtle and include changes in color, tone, activity, and feeling; poor temperature control; or simply a feeling that the newborn is “not doing well” (44). Other early signs may be abdominal distention, apnea, and jaundice, but they may not appear until later stages, or they may even be seen in healthy premature babies. Late signs may include grunting, dyspnea, cyanosis, arrhythmias, hepatosplenomegaly, petechiae, seizures, bulging fontanels, and irritability. In addition, focal signs of meningitis or pneumonia may develop.

Laboratory Criteria in the Placenta and Newborn/Stillborn

Examination of the cord, placenta, or membranes for a leukocytic infiltrate has been suggested as another technique to identify infants at risk for infection (44). However, placental inflammation and/or funisitis are found far in excess of proven cases of sepsis, and the technique is cumbersome. Thus, it is rarely used. In a stillborn who has succumbed to IAI, a heart blood sample should be obtained to attempt to isolate the infecting organism. This technique also should be used in the evaluation of the stillbirth having no apparent cause.

MANAGEMENT

When IAI is diagnosed, there is a need for delivery of the fetus and for antibiotics. With regard to timing of delivery, there has been excellent maternal-neonatal outcome without use of arbitrary time limits. Cesarean delivery has been performed for standard obstetric indications, i.e., not for IAI alone. In nearly all cases, delivery occurred within 8 hours after diagnosis of IAI, and the mean time had been between 3 and 5 hours. No critical interval from diagnosis of amnionitis to delivery could be identified. These observations come mainly from cases at or near term, and it would be desirable to have corresponding data from very premature pregnancies. Cesarean sections rates are higher among patients with IAI, running two to three times greater than in the general population. The reason for the increase most likely results from two observations. First, IAI commonly develops in patients with dystocia as an underlying problem. In the study by Duff et al. (45), approximately 80% of women with IAI received antepartum oxytocin. Second, the uterus with IAI is less sensitive to oxytocin (46).

When a cesarean delivery is necessary, some have advocated the extraperitoneal procedure (47,48), but in a comparative study versus transperitoneal procedure, there was no advantage demonstrated with extraperitoneal section (49). There had been debate as to whether treatment with antibiotics should be initiated during labor or deferred until after delivery to avoid masking neonatal sepsis. The benefits of intrapartum treatment have been well established. Intrapartum initiation of antibiotic treatment improves maternal outcome, decreases neonatal bacteremia, and does not result in delayed sepsis. In 1987, we presented the results of a nonrandomized comparison of intrapartum and immediate postpartum administration of antibiotics (intravenous penicillin G plus intravenous gentamicin) on maternal and neonatal morbidity and mortality (50). Two hundred fifty-seven women with clinically diagnosed IAI and with AF culture were evaluated. With timing of antibiotic treatment at the discretion of the physician, 82% of patients received antibiotics intrapartum; the remaining 18% of women, mainly those with a short interval to delivery, received the antibiotics immediately postpartum. As we expected, the postpartum treatment group had significantly shorter diagnosis to delivery times (1.9 ± 2.1 hours vs. 4.7 ± 4.3 hours; $p < 0.001$). There were no significant differences between the two groups

in distribution of low-birthweight (LBW) infants, maternal bacteremia, mode of delivery, or kinds of organisms in AF. We found no differences in maternal outcome, but the median of neonatal sepsis was significantly lower in the intrapartum treatment group (2.8% vs. 19.6%; $p < 0.001$). Neonatal mortality due to sepsis also was lower in the intrapartum treatment group (0.9% vs. 4.3%), but the difference was not statistically significant. In another retrospective study, 152 women with acute chorioamnionitis received antibiotics before delivery, whereas 160 received either antibiotics after delivery or no antibiotics at all. The rate of neonatal bacteremia was lower when intrapartum antibiotics had been given (2/152 vs. 8/160; $p = 0.06$). In neonates of 35 weeks' gestational age or older, there was a significant reduction in the frequency of GBS bacteremia (0/133 vs. 8/140; $p < 0.05$) (51).

In view of the limitations of these retrospective studies, we carried out a randomized nonblinded study using ampicillin 2 gm intravenously every 6 hours plus gentamicin 1.5 mg/kg intravenously every 8 hours (52). Patients delivered by cesarean section also received clindamycin (900 mg intravenously every 8 hours), beginning after cord clamping, because of the poor response rate of this subset to penicillin and aminoglycoside alone (4). After delivery, one set of blood cultures and a chest x-ray film were obtained from the infants. Cerebrospinal fluid specimens were obtained only from infants with referable signs or symptoms. Then, all infants received the same regimen, ampicillin 7.5 mg/g every 12 hours plus gentamicin 2.5 mg/g every 12 hours, generally within 2 hours of birth. When the neonatal workup was negative, antibiotics were discontinued after 72 hours. If sepsis or pneumonia was diagnosed, treatment was continued for 10 days.

Four weeks after discharge, patient follow-up was obtained to detect any late complications. Our primary endpoint was neonatal sepsis, defined as either bacteremia or death due to infection. Forty-five patients had been enrolled when a decision was made to stop the study. The two groups were comparable with regard to pertinent clinical features (parity, labor duration, ROM and internal monitoring duration, mode of delivery, etc.). The mean diagnosis of IAI to delivery intervals were similar (3.4 ± 2.6 hours vs. 4.1 ± 2.3 hours in the intrapartum and postpartum groups). Maternal outcome was significantly better in the intrapartum treatment groups: lower mean maximum temperature postpartum, mean postpartum hospital stay (4.0 ± 1.0 days vs. 5.0 ± 1.9 days), and nonfebrile days (0.44 ± 0.7 vs. 1.5 ± 2.1); all $p = 0.0.5$. Of greater importance, neonatal outcome was improved (Table 18.3). The four cases of neonatal sepsis in the postpartum treatment group were due to *E. coli* (resulting in death), GBS, *Staphylococcus aureus,* and *Streptococcus pneumoniae.* There were no late complications in any patient.

Characteristic	Maternal Treatment		
	Intrapartum (N = 26)	Postpartum (N = 19)	*p*
Gestational age (wk)*	39.3 ± 2.2	40.1 ± 2.5	
Birthweight (g)	3469 ± 524	3566 ± 582	
Maximum maternal temperature postpartum (°F)	99.8 ± 0.8	100.3 ± 1.1	0.05
Maternal postpartum hospital stay (days)	4.0 ± 1.0	5.0 ± 1.9	0.05
Maternal febrile (days)	0.44 ± 0.7	1.5 ± 2.1	0.05
Early neonatal sepsis [no. (%)]	0	4 (21)	0.03
Neonatal pneumonia or sepsis [no. (%)]	0	6 (32)	0.008
Apgar at 5 min ≤8	0	0	†
Meconium-stained amniotic fluid	3	3	
Neonatal hospital stay (days)*	3.8 ± 1.1	5.7 ± 3.0	0.02

*Data are given as mean ± SD.
†This infant died of sepsis.
From Gibbs RS, Dinsmoor MJ, Newton ER, et al. A randomized trial of intrapartum versus immediate postpartum treatment of women with intraamniotic infection. Obstet Gynecol 1988;74:562.

TABLE 18.3. OUTCOME BY MATERNAL TREATMENT GROUP IN CASES OF INTRAAMNIOTIC INFECTION: RESULTS OF A RANDOMIZED STUDY

Based on these three studies, our conclusion is that intrapartum treatment leads to a decrease in neonatal sepsis, probably a decrease in neonatal death from sepsis, and an improved maternal outcome. These benefits overshadow any theoretical arguments (such as obscuring positive neonatal cultures) against intrapartum treatment in cases of IAI.

Pharmacokinetic studies in late pregnancy show that clindamycin achieves peak concentrations in maternal blood within minutes after injection and in fetal blood shortly thereafter (53). Peak clindamycin concentrations were approximately one half of maternal peaks, but the former were still within therapeutic ranges. In early pregnancy, ampicillin concentrations in maternal and fetal sera are comparable 120 minutes after administration. In late pregnancy, gentamicin also crosses the placenta rapidly, but peak fetal levels may be low, especially if maternal levels are subtherapeutic (53). For the antibiotics noted earlier, levels in AF usually are below fetal serum levels, and peak AF concentrations may be attained only after 2 to 6 hours (53,54). In a novel report of antibiotic concentrations in maternal blood, cord blood, and placental membranes from 25 cases of clinical chorioamnionitis, Gilstrap and colleagues (55) demonstrated that clindamycin, mezlocillin, ampicillin, cefoxitin, and gentamicin all penetrated into cord blood and placental membranes, with achievement of therapeutic concentrations in cord blood.

As noted earlier, the traditional antibiotic approach to treatment has been with combination therapy, primarily a broad-spectrum penicillin with an aminoglycoside, plus clindamycin in some cases (such as cesarean delivery or apparent sepsis). Because of the expense and complexity of such therapy, there has been recent interest in single-drug treatment of IAI. In view of the well-described microbes involved, there would be several reasonable choices for single-agent therapy, but there have not been sufficient comparative trials to recommend alternative single-agent therapy. Recent studies have addressed the issue of duration of antibiotic therapy after delivery in the treatment of chorioamnionitis. In one study, all patients received ampicillin plus gentamicin intrapartum, and those patients delivering vaginally were randomized to receive cefotetan 2 g intravenously as a single dose or in multiple doses every 12 hours for 48 hours (56). Patients randomized to single-dose therapy were discharged from the hospital more quickly (33 vs. 57 hours; $p = 0.001$). Patients who received single-dose therapy had a higher rate of “failed therapy” (11% vs. 3.7%; $p = 0.27$). Although this difference did not achieve statistical significance, a threefold increase in “failed therapy” provides concern about the limitation of single-dose therapy.

In a study of antibiotic therapy after cesarean delivery for chorioamnionitis, all patients received ampicillin in labor and clindamycin and gentamicin one dose each preoperatively. Patients then were randomized to receive no scheduled postoperative antibiotics or clindamycin and gentamicin until they were afebrile (for a minimum of at least 24 hours) (57). No patients in either group developed an abscess or were readmitted for endometritis. Although there was no significant

difference in endometritis (14.8% in those with no routine antibiotic vs. 21.8% in those treated with clindamycin and gentamicin), there was a nonsignificant but still 2.5-fold increase in wound infection rate in patients randomized to no routine antibiotics (5% vs. 1.8% of those randomized to clindamycin and gentamicin postpartum). Based on the limited observations of these two trials and the nagging concerns about “failed therapy” in the first study and the wound infection rates in the second study, it would appear premature to conclude that therapy, after either vaginal or cesarean delivery, in the presence of chorioamnionitis, is unnecessary.

OUTCOME

Short-Term Outcomes

As summarized in Table 18.4, descriptive studies largely from the early 1980s provided outcomes after IAI. Several strong consistent observations were made (4,37,58,59). Maternal outcome was excellent, with bacteriemia occurring in only 2% to 6% (4,37). There were no cases of maternal death or septic shock. Maternal outcome was more complicated in patients having cesarean delivery, which was increased approximately threefold to about 35% to 40%. The increased risk of cesarean section was mainly because of concurrent dystocia. No critical diagnosis to delivery interval was demonstrable (4,59). Specifically, neither prenatal mortality nor maternal complications correlated with more prolonged intervals from diagnoses of chorioamnionitis to delivery, yet all patients delivered within 4 to 12 hours and nearly all patients were receiving intrapartum antibiotics. Although prenatal mortality was relatively high, little of this was directly attributable to infection. Specifically, most of the excessive prenatal mortality was due to accompanying prematurity.

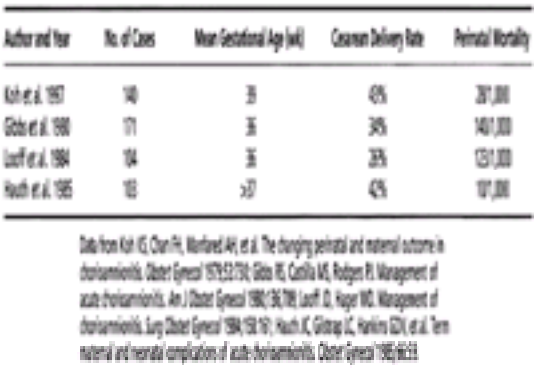


TABLE 18.4. DESCRIPTIVE STUDIES OF OUTCOME IN INTRAAMNIOTIC INFECTION

In 1983, Yoder and colleagues (38) provided a prospective, case-control study of 67 patients with microbiologically confirmed IAI at term. Only one perinatal death was reported, apparently not due to infection. In 49 neonates born of mothers with IAI, cerebrospinal fluid cultures were negative, and there was no clinical evidence of meningitis or enterocolitis. Only 4% had unequivocal radiologic evidence of

pneumonia. Neonatal bacteremia was documented in 8%. There was no significant difference in the frequency of low Apgar scores between the IAI and control groups.

Prior to term pregnancy, neonates have a higher frequency of complications if they are delivered of mothers with IAI. Garite and Freeman (60) noted that the perinatal death rate was significantly higher in 47 preterm neonates with IAI than in 204 neonates with similar birthweights (13% vs. 3%, respectively). The group with IAI also had a significantly higher number with RDS and any diagnosis of infection. The results of this study are summarized in Table 18.5.

	Amnionitis (N = 47)	No Amnionitis (N = 204)	p
Perinatal deaths	6 (13%)	7 (3%)	<0.05
Respiratory distress syndrome	16 (34%)	33 (16%)	<0.01
Total infections	8 (17%)	13 (7%)	<0.05

From Garite TJ, Freeman RK. Chorioamnionitis in the preterm gestation. Obstet Gynecol 1980;56:139.

TABLE 18.5. PERINATAL OUTCOME WITH "AMNIONITIS" IN PRETERM GESTATION 28–34 WEEKS

In a larger study of similar design, Morales (61) reported results of 92 preterm pregnancies complicated by chorioamnionitis and 606 preterm cases without this infection. Chorioamnionitis was accompanied by significant increases in perinatal mortality (25% vs. 6%), RDS (62% vs. 35%), intraventricular hemorrhage (56% vs. 22%), and clinical sepsis (28% vs. 1%). All of these differences were significant ($p < 0.01$ for all) (61). In a large study comparing 123 cases of IAI and 6,769 cases without infection (90% of cases had birthweight >2,500 g), Maberry and colleagues (62) found no differences in mean umbilical artery pH (7.28 in both groups) or rate of acidemia (umbilical artery pH <7.20). More infants from the infected group had low Apgar scores at 1 and 5 minutes, but none in the infected group had metabolic acidemia, seizures, or Apgar scores less than 3. Thus, birth asphyxia is rarely associated with IAI (62).

In a retrospective case-control study, Ferguson et al. (63) reported perinatal outcome after chorioamnionitis. Control infants were the next liveborn infants matched for birthweight within 100 g and gestational age within 2 weeks. Seventy percent of newborns weighed less than 2,500 g. In 116 matched pairs, the authors found more deaths (20% vs. 11%), more sepsis (6% vs. 2%), and more asphyxia (27% vs. 16%) in the chorioamnionitis group. None of these differences was statistically significant. However, it is possible that these are true differences and that this study contains an error.

Further, our group found that LBW infants fared more poorly than did non-LBW

infants when IAI complicated the pregnancy. In 404 cases, LBW infants were delivered in 37 patients (9.2%) and non-LBW infants in 367 (90.8%) (24). We found a significant increase in the incidence of sepsis in the LBW group (16.2% vs. 4.1%; p = 0.005) and in death from sepsis (10.8% vs. 0%; $p < 0.001$). There were no significant differences in intrapartum conditions, intrapartum treatment, or prevalence of GBS, *E. coli,* or enterococci. Although Gram-negative anaerobes were significantly more common in the LBW group (59.5% vs. 31.6%; p = 0.001), no anaerobes were identified in neonatal blood cultures.

Thus, we found that with IAI, outcome in mothers is excellent and that outcome in neonates is good. However, maternal outcome is better when delivery is vaginal and when antibiotics are given intrapartum. Neonatal outcome is better when the infant weighs more than 2,500 g, antibiotics are given in labor, and *E. coli* is not in the AF.

Patients with amnionitis have a greater likelihood of abdominal delivery, generally 30% to 43% in recent studies (4,37,38). This increase may result from an adverse effect of the infection on uterine function. Duff and colleagues (45) reviewed the labor records and internal fetal monitoring tracings of 65 term patients who entered labor spontaneously and then developed clinical chorioamnionitis. In 82% of these patients, there was a positive AF culture with high-virulence organisms. Overall, chorioamnionitis developed more commonly in patients with complicated labor. For example, decreased uterine contractility and oxytocin administration were noted in 75%, and cesarean delivery was performed in 34%. Mean interval from diagnosis of chorioamnionitis to delivery was approximately 4 hours. In the group requiring cesarean delivery, uterine activity in the 3 hours prior to delivery was 146 Montevideo units. In the group delivering vaginally, mean activity was 167 Montevideo units in this interval. Mean maximum oxytocin dose was approximately 6.5 mU for the entire group. The most common fetal heart rate abnormalities were diminished variability (77%) and tachycardia (67%). Only one infant had a 5-minute Apgar score below 7. The authors concluded that cesarean sections were not simply due to physician anxiety, but that chorioamnionitis has an inhibitory effect on labor.

In a follow-up report, Silver and colleagues (46) from San Antonio concluded the course of labor in high-risk nulliparous with serial AF cultures. All patients were afebrile at the time of AF collection but had membrane rupture for more than 12 hours. Compared with patients with low-virulence isolates (n = 16), those with high-virulence isolates (n = 19) had lower cervical dilation despite an increased maximum oxytocin dose. Controlling for birthweight, labor length, and use of epidural anesthesia, magnesium sulfate, and oxytocin, it was observed that patients with high-virulence bacteria also had a higher cesarean section rate (58% vs. 25%; p = 0.05). The authors concluded that their observations supported a causal relationship between high-virulence bacteria in the AF and poor cervical response to oxytocin in patients at risk for IAI.

In sum, IAI has a significant adverse effect upon the mother and neonate. Outcome is largely dependent on the organisms in AF (with *E. coli* and GBS more likely to result in maternal or neonatal bacteremia), birthweight (with LBW infants faring more poorly), and timing of antibiotic therapy (with intrapartum administration improving outcome).

Long-Term Outcomes

Hardt and colleagues (64) followed preterm infants (<2,000 g) born after chorioamnionitis and found a significantly lower mental development index (Bayley score) compared with that of preterm controls.

Traditional complications of IAI have been maternal and neonatal sepsis, neonatal pneumonia and meningitis, and neonatal death. Recent studies indicate that complications of IAI should be expanded to include periventricular leukomalacia, cerebral palsy, RDS, and perhaps other neonatal complications. The hypothesized mechanism is that ascending infection leads to placental and congenital infection. This results in an overexuberant production of inflammatory cytokines that leads to cell damage. Evidence for these expanded neonatal complications after IAI are as follows. (i) Intrauterine exposure to maternal or placental infection is epidemiologically associated with an increased risk of cerebral palsy. (ii) Levels of inflammatory cytokines are increased in the AF of infants with brain white matter lesions or RDS. (iii) Experimental intrauterine infection has led to brain white matter lesions in rabbits.

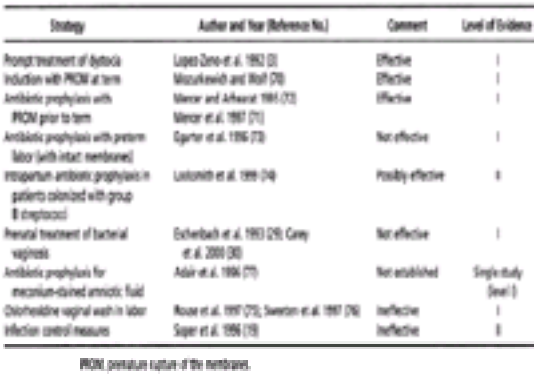
Recent epidemiologic studies have demonstrated an increased risk of cerebral palsy among infants delivered from pregnancies complicated by fever in labor, clinically chorioamnionitis, or histologic chorioamnionitis (65). In an observational cohort of singletons with birthweight between 500 and 1,500 g, clinical chorioamnionitis was significantly associated with an increased risk of periventricular leukomalacia, the precursor lesion for cerebral palsy (66).

In complicated preterm pregnancies, elevated levels of amnionic fluid interleukin-6 and interleukin-1b correlated with an insignificant increased odds ratio for brain white matter lesions (67). Among preterm infants, elevated amnionic fluid cytokines, tumor necrosis factor alpha, and interleukin-6 were significantly associated with development of RDS in a case-control study (68). Respiratory distress syndrome also was significantly associated with a positive amnionic culture and with severe histologic chorioamnionitis.

Finally, in a rabbit model of “chronic infection” lasting for 5 days, intrauterine infection, as documented by a positive intrauterine culture, was significantly associated with rabbit pup brain white matter lesions (8% in pups with infection vs. 0% in pups without infection; $p < 0.005$) (69). Thus, there is intriguing information developing that intrauterine exposure to bacteria, whether evident through clinical or subclinical infection, is an important precursor for major neonatal sequelae. It remains for a cause-and-effect relationship to be established and to determine whether appropriate interventions can be developed.

PREVENTION

Within the last few years, several intervention strategies for the purpose of preventing clinical intraamniotic infection have been evaluated. These are summarized in Table 18.6.



Strategy	Author and Year (Reference No.)	Comment	Level of Evidence
Prompt treatment of dystocia	Lopez Zeno et al. 1992 [2]	Effective	I
Induction with PROM at term	Mozurkewich and Wolf [70]	Effective	I
Antibiotic prophylaxis with PROM prior to term	Mercer and Arheart 1995 [72]; Mercer et al. 1997 [71]	Effective	I
Antibiotic prophylaxis with preterm labor (with intact membranes)	Egarter et al. 1996 [73]	Not effective	I
Intrapartum antibiotic prophylaxis in patients colonized with group B streptococci	Lusiomich et al. 1999 [74]	Possibly effective	II
Prenatal treatment of bacterial vaginosis	Eschenbach et al. 1993 [29]; Carey et al. 2000 [30]	Not effective	I
Antibiotic prophylaxis for meconium-stained amniotic fluid	Adair et al. 1996 [77]	Not established	Single study (level I)
Chlorhexidine vaginal wash in labor	Rouse et al. 1997 [75]; Swenson et al. 1997 [76]	Ineffective	I
Infection control measures	Soper et al. 1996 [78]	Ineffective	II

PROM, premature rupture of the membranes.

TABLE 18.6. POTENTIAL PREVENTION STRATEGIES FOR CLINICAL INTRAAMNIOTIC INFECTION

First, because IAI is often a complication of prolonged labor, one might expect that early diagnosis of labor abnormalities and early intervention would decrease IAI. In a large randomized trial conducted at Northwestern University, patients were treated by “active management” (consisting of early amniotomy and early institution of oxytocin at an initial rate of 6 mU/min) or traditional management. Among other benefits of this approach, the investigators noted a reduction in the average length of labor by 1.66 hours ($p < 0.0001$) and a reduction in clinical chorioamnionitis (9.9% vs. 4.6%; $p < 0.01$). The cesarean delivery rate also was significantly decreased (14.1% vs. 10.5%) after controlling for confounding variables (odds ratio, 0.57; 95% confidence interval, 0.36–0.95). The major benefits were attributed to early amniotomy and early use of oxytocin, rather than to the higher oxytocin dose (3).

Second, in a metaanalysis of 23 studies that included nearly 7,500 patients, it was concluded that conservative management may result in more maternal infection than immediate induction with either oxytocin or prostaglandins (70). This metaanalysis also is discussed in the Chapter 17.

Third, broad-spectrum antibiotics in preterm PROM is another strategy that has significantly reduced the risk of clinical chorioamnionitis (71,72). This strategy also is discussed in detail in Chapter 17. Fourth, in comparison to the situation with preterm PROM in preterm labor (but with intact membranes), broad-spectrum antibiotics have *not* been demonstrated to decrease chorioamnionitis. In the metaanalysis performed by Egarter and colleagues (73), neither chorioamnionitis nor endometritis was significantly reduced. Fifth, national guidelines have been established for the prevention of prenatal GBS infection through intrapartum prophylaxis. A potential side benefit is a reduction in chorioamnionitis and possibly endometritis. An historically controlled report has shown that, under a plan of universal screening, there was a small but significant reduction in chorioamnionitis compared to historical periods in which either a risk factor-based approach was used or selective screen (74). Specifically, when universal screening was applied (1996 to 1998), the rate of chorioamnionitis was approximately 5.2%, compared with rates of 7% to 8% in the two previous historical (1991 to 1993 and 1993 to 1996).

Sixth, although prenatal detection and treatment of BV has been an effective strategy

in some trials for reduction of recurrent preterm birth, this strategy has not been effective in preventing chorioamnionitis in randomized clinical trials of BV with clindamycin vaginal cream. Although the clindamycin vaginal cream significantly reduced the likelihood of BV, there was not a significant reduction in amnionitis (29). Further, in the recent Maternal-Fetal Medicine Units Network Trial of BV treatment with oral metronidazole, prenatal treatment was not associated with a reduction in intraamniotic infection (30).

Seventh, chorioamnionitis is associated with a significant increase in meconium staining amnionic fluid. Accordingly, in a single randomized trial, administration of ampicillin-sulbactam to patients with meconium-stained AF was associated with a significant reduction in IAI (23% vs. 7%; $p = 0.02$), but this was not associated with a significant reduction in maternal stay or neonatal sepsis. Overall, the benefit in term patients was not clear, considering the additional antibiotic exposure through prophylaxis, the limited effect demonstrated, and the relatively small nature of this study. Eighth, because chlorhexidine vaginal washes have been evaluated as prevention strategy for ascending prenatal GBS infection, it was suspected that chlorhexidine vaginal washes might prevent clinical chorioamnionitis. However, two randomized trials demonstrated that this was not effective (75). Ninth, imposing infection control measures has been evaluated to prevent chorioamnionitis (19). Despite the intrinsic appeal of such an approach, this was not an effective strategy. A summary of measures to be applied to current practice to prevent chorioamnionitis is shown in Box 1.

Box 1

Clinical Measures to Prevent Chorioamnionitis

- Identify dystocia promptly and treat hypotonic dysfunctional labor promptly with oxytocin.
- In patients with PROM at term, induce labor with either oxytocin or prostaglandin preparations.
- In patients with preterm PROM and without contractions, give broad-spectrum antibiotics such as ampicillin-amoxicillin plus erythromycin for 7 days.
- Follow CDC/ACOG guidelines for prevention of perinatal GBS infection.
- For patients with preterm labor but without rupture of membranes, perinatal GBS guidelines should be followed, but broad-spectrum antibiotics given to prevent chorioamnionitis have not been effective.

Based on the association of BV with IAI, prenatal therapy for this lower genital infection might reduce the risk for IAI. Yet, in one controlled trial (29), no such reduction was observed. However, in that trial, patients were treated one time for 7 days at the beginning of the third trimester. It is probable that later, longer, or repeated treatment of BV may be needed to achieve a decrease in IAI. For the present, antepartum treatment of BV to prevent IAI in asymptomatic women is not indicated.

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19

SUBCLINICAL INFECTION AS A CAUSE OF PREMATURE LABOR

Preterm birth, with its subsequent morbidity and mortality, is the leading perinatal problem in the United States. Infants born before the 37th week of gestation account for approximately 6% to 9% of all births but 70% of all perinatal deaths and half of long-term neurologic morbidity. In most cases, the underlying cause of premature labor is not evident, and attempts may be made to arrest premature uterine contractions. However, this symptomatic treatment (tocolysis) is not indicated in many patients because of serious fetal or maternal disease. In other patients, tocolytic agents are ineffective, especially when labor is advanced or the membranes are ruptured (Fig. 19.1) (1,2). Even when clinical conditions are optimal for use of tocolytics, recent trials showed that their efficacy is limited (3), and their use is accompanied by potentially serious adverse effects. Thus, despite widespread use of tocolytics, no decrease in low birthweight (LBW) has been observed in the last 20 years (Fig. 19.2) (4). It is likely that therapy directed at preventing or treating underlying causes would be more successful.

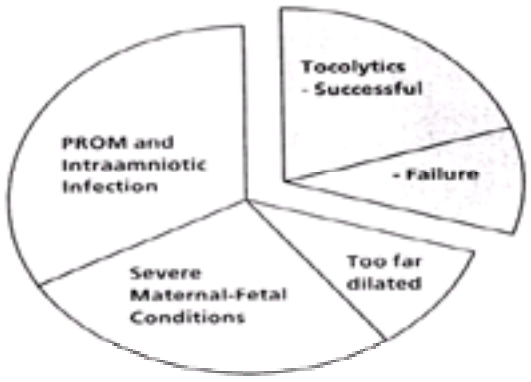


FIGURE 19.1. Most patients presenting in premature labor or with premature birth are not candidates for tocolytics, or tocolytics are unsuccessful. (After Minkoff H. Prematurity: infection as an etiologic factor. *Obstet Gynecol* 1983;62:137, and Tejani

NA, Verma UL. Effect of tocolysis on incidence of low birth weight. *Obstet Gynecol* 1983;61:556.)

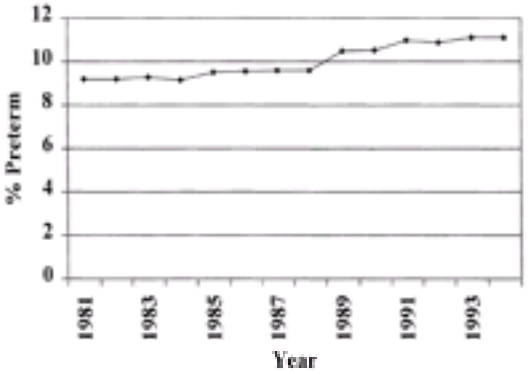


FIGURE 19.2. Rates of preterm birth in the United States. (Data from Monthly Vital Statistics, 1994. National Center for Health Statistics. Advance report of final natality statistics, 1994. *Monthly Vital Statistics Report* 1996;44[11S];75.)

Evidence from many sources links preterm birth with symptomatic infections. Untreated bacteriuria in pregnancy results in acute pyelonephritis in 20% to 40% of patients, and pyelonephritis has a seriously increased risk of fetal morbidity and mortality. In the preantibiotic era, many systemic maternal infections, such as pneumonia, often led to premature birth. In the last decade, great interest has been generated by subclinical infection as a cause of premature labor, and much new information has been presented, as categorized in Table 19.1. In the past 5 years, additional exciting information has suggested that subclinical infection is responsible not only for preterm birth, but also for many serious neonatal sequelae, including periventricular leukomalacia, cerebral palsy, respiratory distress syndrome, and even bronchopulmonary dysplasia and necrotizing enterocolitis. In addition, numerous trials have been reported and have provided a clearer direction on how to use antibiotics in clinical practice to prevent preterm birth.

1. Histologic chorioamnionitis is increased in PTB
2. Clinical infection is increased after PTB
3. There are significant associations of some lower genital tract organisms/infections with PTB or preterm premature rupture of the membranes
4. There are positive cultures of amniotic fluid or membranes from some patients with preterm labor/PTB
5. There are markers of infection in PTB
6. Bacteria or their products induce PTB in animal models
7. Some antibiotic trials have shown a lower rate of PTB or have deferred PTB

PTB, preterm birth.

TABLE 19.1. EVIDENCE FOR SUBCLINICAL INFECTION AS A CAUSE OF PRETERM BIRTH

The Infection Hypothesis

The hypothesis linking subclinical infection and premature birth is as follows. (a) Microbes or microbial toxins such as endotoxin (lipopolysaccharide) enter the uterine cavity during pregnancy, primarily by the ascending route from the lower genital tract but, on occasion, by the bloodborne route from a nongenital focus (Fig. 19.3). (b) An interaction occurs between the microbes or their products, most likely in the decidua or possibly in the membranes. (c) This interaction, probably mediated through a cytokine cascade, leads to prostaglandin production or directly to uterine muscle contraction. (d) Cervical dilation occurs, and more microbes enter into the uterus (Fig. 19.4). (e) Premature birth results. These interactions are shown in an expanded diagram in Fig. 19.5. We now critique the evidence.

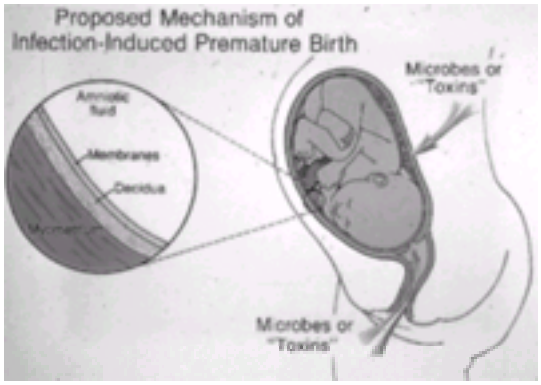


FIGURE 19.3. Proposed mechanism of infection-induced premature birth. Microbes or microbial toxins enter the uterine cavity by an ascending or bloodborne route. An interaction then occurs, most likely in the decidua, to release cytokines and prostaglandins.

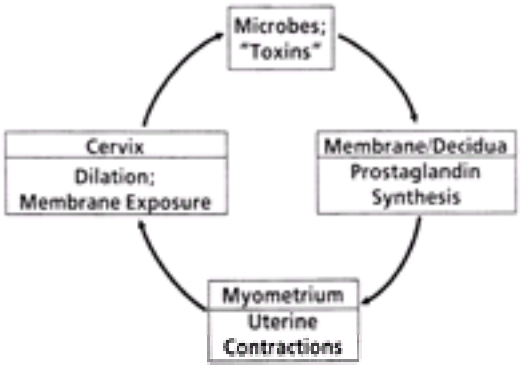


FIGURE 19.4. Diagrammatic representation of the proposed links between infection and preterm uterine contractions.

FIGURE 19.5. Potential pathways from choriodecidual bacterial colonization to preterm delivery. (From ref. 30.)

Histologic Chorioamnionitis Is Increased in Preterm Birth

One of the most consistent observations linking subclinical infection and preterm birth is the increased likelihood of histologic chorioamnionitis in cases of preterm birth. For example, in a large study of 3,600 placentas, histologic chorioamnionitis (polymorphonuclear infiltrates in the membranes) was observed in 11% of membranes overall (5). For infants weighing less than 2,500 g, the likelihood of chorioamnionitis increased to 20%; for infants weighing less than 1,800 g, chorioamnionitis increased to 36%; and for infants less than 1,000 g, chorioamnionitis was observed in fully 50% of membranes. Most cases of histologic chorioamnionitis are caused by infection. In preterm membranes, Hillier and colleagues (6) have found a very strong association between positive membrane cultures and degree of membrane infiltration. When birthweight was greater than 3,000 g, the percentage of placentas showing histologic chorioamnionitis was less than 20%; when birthweight was less than 1,500 g, the percentage was 60% to 70% (Fig. 19.6).

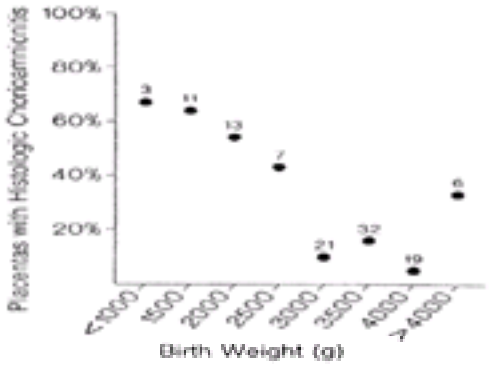


FIGURE 19.6. Placentas with histologic chorioamnionitis by gestational age. (From Hillier SL, Martius J, Krohn M. A case controlled study of chorioamnionitis infection and histologic chorioamnionitis. *N Engl J Med* 1988;3198:972–978, with permission.)

Clinical Infection Is Increased After Preterm Birth

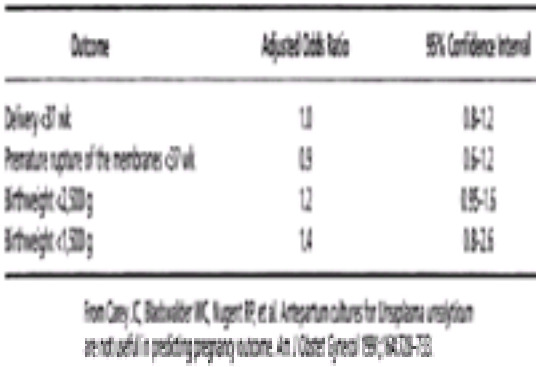
Another consistent observation is that clinically evident infection is increased in both neonates and mothers after preterm birth. For example, sepsis and meningitis are increased threefold to tenfold in preterm infants (7). Less widely recognized is the increase in maternal infection after preterm birth. In a review of a large number of births, Daikoku et al. (8) found that fever before delivery was increased in preterm versus term deliveries (6.3% vs. 1.4%) and that endometritis also increased (15.5% vs. 6.8%). In a study of 8,400 term and 1,250 preterm births at the University of Colorado, clinical chorioamnionitis, postpartum endometritis, and neonatal infection were all significantly increased among preterm pregnancies, even after correction for the presence of premature rupture of the membranes (PROM) (9). These representative observations may be interpreted to mean that subclinical infection was the cause of the preterm birth and that the infection became clinically evident during or shortly after birth. However, this causal relationship is conjectural. An alternative explanation is that the preterm infant with well-known decreases in host defenses is more susceptible to infection developing after delivery. The alternative explanation for excess maternal infection accompanying preterm birth is that these mothers have important confounding factors (such as prolonged membrane rupture) complicating the delivery.

There Are Associations of Preterm Birth or Premature Rupture of the Membranes with Various Maternal Lower Genital Tract Isolates or Infections

Several surveys have found statistically significant associations between lower genital infection and adverse pregnancy outcome. *Ureaplasma urealyticum* in the lower genital tract and/or urinary tract has been associated with LBW infants (10), but this study did not control for other organisms. In couples with histories of pregnancy wastage and with positive genital or urinary cultures for genital mycoplasmas, doxycycline treatment before conception reduced the pregnancy loss rate to 48%, compared with a loss rate of 96% in the “no treatment” group. Erythromycin (250 mg four times a day from the second or third month until the end of pregnancy) further reduced the pregnancy loss rate to 16%. However, the trial was small and poorly

controlled (11).

Carey et al. (12) reported no associations of *U. urealyticum* with any adverse pregnancy outcome in a large collaborative study. This study included more than 4,500 patients and tested for lower genital tract microbes including bacteria, mycoplasmas, and chlamydia. The analysis shown in Table 19.2 excludes patients with either group B streptococci (GBS) or chlamydia, confounding organisms that have been implicated in preterm birth. Interestingly, *U. urealyticum* in the lower genital tract is *not* associated with LBW/preterm pregnancies, but this organism is one of the most commonly isolated in the amniotic fluid of women in preterm labor.



Outcome	Adjusted Odds Ratio	95% Confidence Interval
Delivery <37 wk	1.0	0.8–1.2
Premature rupture of the membranes <37 wk	0.9	0.6–1.2
Birthweight <2,500 g	1.2	0.85–1.5
Birthweight <1,500 g	1.4	0.8–2.6

From Carey JC, Klebanoff MC, Hauger RP, et al. Antepartum cultures for Ureaplasma urealyticum are not useful in predicting pregnancy outcome. Am J Obstet Gynecol 1991;164:1328–1333.

TABLE 19.2. UREAPLASMA UREALYTICUM AND ADVERSE PREGNANCY OUTCOME (N = 4,576)

Lower genital infection with *Chlamydia trachomatis* has been implicated in adverse pregnancy outcome. Pregnant women with endocervical *C. trachomatis* infection were significantly more likely to deliver stillborns or infants succumbing to neonatal deaths (6/18 [33%]) than were women not infected in early pregnancy (8/23 [34%]) (13). In a matched cohort analysis of these data, the authors reported a perinatal mortality risk ratio for pregnancies with versus pregnancies without antepartum chlamydial infection of 10.18 ($p = 0.004$, one-tailed test). There also was a difference in duration of gestation between *Chlamydia*-positive women and the 238 uninfected women as determined by analysis of covariance ($p < 0.001$). Gravett et al. (14) found a significantly higher preterm delivery rate in patients with antepartum cervical chlamydial infection (36% vs. 12%; $p < 0.01$). However, in five other surveys totaling nearly 9,000 patients, no significant association was seen between antepartum cervical infection with chlamydia and preterm delivery (15,16 and 17).

It is possible that a subpopulation of women with chlamydial infection, namely, those with antichlamydial immunoglobulin M (IgM) in their sera, are the group at true risk of preterm birth. In a study of 1,365 women in Arizona, Harrison and colleagues (16) found that women with a positive chlamydial culture and a positive serum IgM had preterm delivery in 24% of cases, which is significantly greater ($p = 0.025$) than either women with a positive chlamydial culture but with a negative serum IgM or women with a negative serum IgM or women with a negative chlamydial culture (2% and 6%, respectively). These findings were confirmed in a study from San Francisco

(17). As shown in Table 19.3, women with both a positive chlamydial culture and a positive serum IgM were at significantly increased risk for preterm birth and PROM.

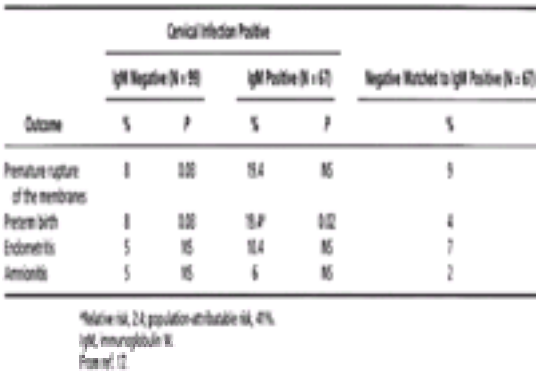


TABLE 19.3. CHAMYDIA TRACHOMATIS AND PREGNANCY OUTCOME

An association between maternal GBS colonization and premature birth has not been found consistently (18,19). In a large National Institutes of Health (NIH)-sponsored investigation of approximately 13,000 women, pregnancy outcome was investigated for three groups of women: those without GBS, those with high-density lower genital tract colonization, and those with low-density colonization. Compared with the 10,295 noncolonized women, those with heavy GBS colonization had a small but significant increase in risk for LBW (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.01–1.5). There was no significant increase in other adverse outcomes, including preterm birth, for heavily colonized women. Women with light colonization were not at an increased risk for any adverse outcomes (20). In a randomized treatment trial of erythromycin versus placebo in GBS-colonized women, erythromycin use was not shown to be effective in prolonging gestation or increasing birthweight (21).

Data are contradictory regarding an association between *Trichomonas vaginalis* and premature birth. Among 115 gravid adolescents in Baltimore, *T. vaginalis,* which was recovered vaginally from 34%, was associated with LBW and early gestational age at birth (22). Mason and Brown (23) had reported a similarly high vaginal infection rate with *T. vaginalis* in 184 women but had found no association with adverse pregnancy outcome. In a small series in Brooklyn, Minkoff et al. (19) found *T. vaginalis* in 22% of 18 women who developed preterm labor and failed tocolysis and in 11% of 17 women who had preterm labor but with successful tocolysis. In comparison, 14% of 183 gravid women with term deliveries had *T. vaginalis.* These differences were not statistically significant (19). However, in the large Vaginal Infections and Prematurity Study, lower genital tract carriage of *T. vaginalis* at mid pregnancy was significantly associated with preterm LBW. Preterm LBW occurred in 7.1% of women with *T. vaginalis* compared with 4.5% of women without *T. vaginalis* (OR, 1.6; 95% CI, 1.3–1.9) (24,25).

Considerable data have implicated anaerobes in preterm labor. Minkoff and colleagues (19) found vaginal colonization with *Bacteroides* sp associated with

preterm delivery (relative risk [RR], 1.4; $p < 0.03$), preterm PROM (RR = 2.8; $p < 0.01$), and LBW (RR, 1.6; $p < 0.04$). Other investigators also showed significant associations between *Bacteroides* sp and preterm labor or preterm delivery (24). Further, bacterial vaginosis (BV) is a vaginal condition characterized by a predominance of anaerobes (see Chapter 12). Studies have repeatedly demonstrated an association between BV and preterm birth. Overall, patients with BV have an approximately twofold to threefold increase in spontaneous preterm delivery (25,26,27,28 and 29). It is unclear whether BV causes preterm delivery by leading to intrauterine subclinical infection or BV acts locally in the lower genital tract infections, as it is associated with increased concentrations of elastase, mucinase, and sialidase (30). In a cohort of 10,397 pregnant women, BV was associated with preterm LBW (OR, 1.4; 95% CI, 1.1–1.8) after multivariate analysis controlling for other factors and *C. trachomatis* (25).

Untreated pyelonephritis has been associated with an approximately 24% risk of preterm delivery (24). In a metaanalysis, Romero and Mazor (31) concluded that asymptomatic bacteriuria had a 60% higher rate in LBW (95% CI, 1.4–1.9) and a 90% higher rate of preterm delivery (95% CI, 1.3–2.9). Untreated gonococcal infection of the lower genital tract also has been associated with preterm with preterm delivery (24).

Organisms Are Found in Amniotic Fluid/Membranes/Decidua of Patients in Premature Labor

Many studies reported amniotic fluid cultures obtained by amniocentesis from asymptomatic women in premature labor (26,32,33,34,35,36,37,38,39,40 and 41). The range of positive cultures is 3% to 24%, an eightfold difference. Part of these widely ranging results may be explained by patient selection. For example, it is possible that studies reporting a low culture positivity rate (3%–4%) performed amniocentesis on patients in “prodromal” or “false” premature labor. An alternative explanation of these findings is that the bacteria are not actually the cause of the preterm labor but the result. To date, there has not been a comparative study of amniotic fluid cultures (obtained by amniocentesis) from patients in preterm and term labor with similar cervical dilation and effacement. Women in preterm labor and with bacteria or *Candidia albicans* in the amniotic fluid were significantly less likely to respond to tocolytics and delivered promptly (26).

The most likely route for bacteria to enter the amniotic fluid or deciduas of patients in preterm labor is an ascending path through the vagina and cervix. It also is possible to speculate that bacteria may enter the uterine cavity hematogenously through spread via the placenta; by contamination at the time of instrumentation, such as amniocentesis or chorionic villus sampling; or even by spread from the abdominal cavity via the fallopian tubes (30). Potential sources of organisms for hematogenous spread include bacteremia from renal or periodontal disease.

Among women in spontaneous preterm labor with intact membranes, genital mycoplasmas and anaerobic organisms, as well as *Gardnerella vaginalis* (the so-called BV organisms), are those organisms most commonly found in the amniotic fluid. Sexually transmitted organisms, such as *Neisseria gonorrhoeae* and *C. trachomatis,* are rarely found in the amniotic fluid, and GBS and *Escherichia coli* are found only occasionally. When organisms from the lower genital tract ascend into the uterine cavity, it is most likely that the initial site is in the choriodecidual space. In

some women, bacteria cross the intact membranes into the amniotic fluid; in some cases, the fetus becomes infected (30).

Women in preterm labor with the highest likelihood of having a positive culture of the amniotic fluid are those patients in very early preterm labor. There is no ready explanation for this consistent observation, but it may be speculated that intrauterine infection occurs early in pregnancy—or even preceded the pregnancy—and may remain without clinical detection for months. Evidence to support such chronic infection arises from studies showing positive cultures for ureaplasmas from amniotic fluid taken for routine chromosome analysis at mid pregnancy. In addition, high fetal fibronectin concentrations in the lower genital tract at 24 weeks (possibly suggestive of an upper genital tract infection) have been associated with development of chorioamnionitis almost 2 months later (30).

There Are “Markers” of Infection in Premature Labor

As noted earlier, when premature labor is induced by infection, the primary site of infection is not the amniotic fluid, but the decidua or membranes. Thus, looking for organisms in amniotic fluid may be an insensitive diagnostic technique. Accordingly, recent studies have sought potentially more sensitive markers of infection. These markers have been identified both in women presenting with signs and symptoms of preterm labor as well as in asymptomatic patients (usually at risk for preterm labor) during prenatal care. As shown in Table 19.4, these specimens have been obtained from the amniotic fluid, the vagina and cervix, and the serum. Despite the variety of these markers, relatively few are clinically useful. Among patients in preterm labor, a low amniotic fluid glucose correlates well with the likelihood of a positive culture. Observing bacteria or white cells on a Gram stain also is useful, as is absolute white blood count in the amniotic fluid. Among the cytokines, an elevated amniotic fluid interleukin-6 level probably is the most sensitive marker for infection but is not yet widely available for clinical use.

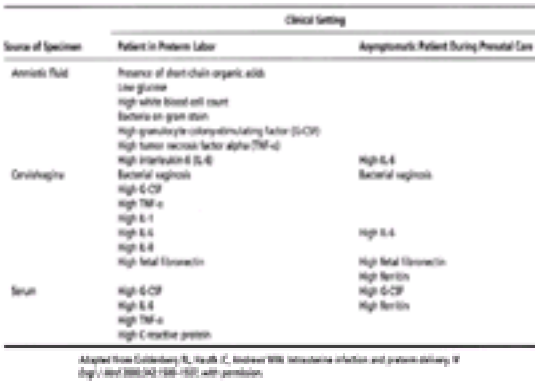


TABLE 19.4. MARKERS OF INTRAUTERINE INFECTION DURING PREGNANCY

In view of the association between BV and intrauterine infection (both in patients in preterm labor as well as in high-risk asymptomatic patients during prenatal care), one useful strategy to prevent preterm labor is the selective treatment of BV in

women who are at very high risk for preterm birth (such as women who had a previous delivery complicated by preterm labor or preterm PROM).

It has not been established that the results of amniotic fluid testing in patients in preterm labor improve the outcome of pregnancy. Thus, we use amniocentesis selectively among patients in preterm labor. Examples of such cases are patients who may have subtle signs and symptoms of infection, patients who do not respond well to tocolytics, and patients with recurrent preterm labor.

The data may be summarized as follows (Fig. 19.5) (23,42,43,44,45,46 and 47). First, prostaglandins are involved in labor at term and most likely before term as well. Second, a number of common genital tract bacteria elaborate phospholipase A^2, an enzyme leading to prostaglandin synthesis. Genital tract anaerobes were among the species with greatest production. Third, *in vitro* inflammatory cytokines such as interleukins and tumor necrosis factor stimulate gestational tissues to produce prostaglandins and metalloproteases. Fourth, amniotic fluid concentrations of prostaglandins and cytokines are increased in some patients in preterm labor, such as those with evidence of infection or with poor response to tocolytics. Fifth, *in vitro,* interleukin-1 stimulates uterine muscle contractions. Sixth, bacterial products such as endotoxin also stimulate uterine muscle contraction *in vitro* (24). Seventh, the fetus may contribute to the link between infection and preterm labor. For example, increased adrenal cortisone production (triggered by infection) also may lead to increased prostaglandins.

Thus, the combination of increased fetal adrenal cortisol production, increased prostaglandin production, and increased cytokines and chemokines may lead to myometrial contractions, membrane rupture, cervical ripening, and preterm elivery (30).

Bacteria/Bacterial Products Induce Preterm Birth in Animals

As outlined in this chapter, the human evidence that infection is a cause of preterm is circumstantial. Animal models have provided direct evidence in the rabbit, monkey, and mouse.

Our group and others have shown that the rabbit model produces rapid, reproducible intrauterine infection accompanied by maternal sepsis, pregnancy loss, and histologic evidence of inflammation after inoculation of *E. coli* or other organisms (48,49). Bacterial inoculation intracervically was followed by dramatic increases in amniotic fluid concentrations of prostaglandins, interleukin-1, and tumor necrosis factor, all mimicking the human situation (49).

In this ascending model of infection, we found that use of antibiotics is effective if given within 2 hours of intrauterine inoculation and up to 12 hours after intracervical inoculation (50).

Primate models are attractive because of their similarities to humans in the number of fetuses (usually singletons), anatomy, and placentation. In Rhesus monkeys, Gravett and colleagues (51) showed a relationship between amniotic fluid infection, cytokines, prostaglandins, and uterine activity in three chronically instrumented animals at 130 days' gestation by inoculating GBS. Increases in uterine activity were

detected between 14 and 36 hours after inoculation in three monkeys. Sequential sampling of the amniotic fluids showed increases in bacterial count and corresponding increases in interleukin-1b and prostaglandins E^2 and F^2a over time after inoculation. The increases in cytokines and prostaglandins appeared before uterine activity (51).

There has been interest in the mouse model because of its short gestation and low cost. Romero et al. (52) demonstrated that systemic administration of human recombinant IL-1b led to vaginal bleeding and preterm delivery, whereas administration of saline did not. They later demonstrated that IL-1 receptor antagonist (1 mg) could block the preterm labor induced by IL-1 (10 µg) (53).

Thus, animal models have shed light on the evolving picture of infection as a cause of preterm labor (54). Future work will enable us to obtain systematic information not available from study of humans with preterm labor.

Some Antibiotic Trials in Pregnancy Have Reduced Prematurity or Low Birthweight Rates

In view of these data, studies of antibiotic treatment in pregnancy are especially interesting. Trials may be classified as one of three designs: (i) those conducted prenatally in patients viewed as being at high risk for preterm delivery; (ii) those conducted among women in preterm labor with intact membranes, as adjuncts to tocolytic therapy; and (iii) those conducted among women with preterm PROM (55).

Early studies of the first design type were published 30 years ago (56,57). In a later treatment study, the percentage of LBW deliveries among women treated with erythromycin for 6 weeks in the third trimester was lower than the percentage of women given a placebo. The decrease was from 12% (10/84) in the placebo group to 3% (2/64) in the erythromycin group ($p = 0.063$). The infants in the placebo group weighed significantly less (3,187 vs. 3,331 g; $p = 0.041$). Because of a low isolation rate for *C. trachomatis* (4%–6%) in the population, the authors concluded that it was unlikely that the erythromycin effect was primarily explained by an antichlamydial effect. It was interesting, however, that repeated vaginal cultures, taken during and after treatment, showed “only a slight reduction in the carriage of mycoplasmas as a consequence of treatment.” These data were updated and reported separately (57).

In a much larger multiinstitutional study, however, antepartum oral erythromycin or placebo was administered to pregnant women with *U. urealyticum* in vaginal cultures. (Patients with *C. trachomatis* or GBS were excluded from this analysis). Medications were given from early third trimester until 35 weeks (or delivery). With nearly 500 women in each arm of this randomized clinical trial, there was no significant difference in birthweight, LBW rate, or prematurity rate (58). Patients receiving erythromycin for 4 weeks had a rate of *Ureaplasma* colonization similar to that of patients receiving placebo. This large randomized trial provides compelling evidence that treatments aimed at eradicating lower genital tract *U. urealyticum* during prenatal care are of no value in preventing preterm birth in women at risk on the basis of epidemiologic risk factors only. Thus, treatment of *U. urealyticum* in pregnancy to prevent prematurity remains experimental.

There have been two nonrandomized studies in which patients with cervical *C.*

trachomatis infection were evaluated for the effect of antibiotic treatment on pregnancy outcome. In the first study, patients successfully treated for *C. trachomatis* had significantly lower rates of PROM and premature labor than patients who failed to have *C. trachomatis* eradicated (59). In the second report, adverse outcome was assessed among three large groups: *C. trachomatis* positive but untreated (n = 1110); *C. trachomatis positive* and treated (n = 1327); and *C. trachomatis* negative (n = 9111) (60). The *C. trachomatis*-positive but untreated group had PROM and LBW significantly more often and ha d a higher perinatal mortality than the other two groups. In a randomized treatment trial of *C. trachomatis* infection, the rate of LBW pregnancies was reduced in three of the five centers but not significantly reduced in the remaining two (61). After these trials were completed, it became the standard of care to treat women with *C. trachomatis* infection, not as much to prevent preterm labor but to prevent spread of sexually transmitted disease.

Several reports have noted decreases in premature birth among high-risk women with BV treated during prenatal care. Hillier et al. (25) reported an observational study, and McGregor et al. (62) reported a prospective two-phase trial in a city hospital. Morales et al. (63) conducted a randomized trial in women with a previous preterm birth. Compared with the placebo group, patients in the metronidazole group had fewer preterm births (39% vs. 18%; $p < 0.05$). Subsequently, McDonald and colleagues (64) performed a randomized treatment trial of metronidazole in low-risk women who had “bacterial vaginosis flora.” These women had a heavy growth of *G. vaginalis* or BV on Gram stain. When treated with metronidazole 400 mg or placebo twice a day for 2 days at 24 weeks (with repeat treatment at 29 weeks if needed), overall there was no significant reduction in the rate of spontaneous preterm birth. However, among the subset of patients who had previous preterm birth, there was a significant reduction in the rate of preterm delivery from 47% in the placebo group to 14% in the metronidazole group. Finally, in a randomized treatment trial of metronidazole to prevent preterm delivery in women with asymptomatic BV, Carey and colleagues (65) randomized patients to either metronidazole 2.0-g doses at 16 to 24 weeks and at 24 to 30 weeks or a corresponding regimen for a placebo. Comparing the 953 patients in the metronidazole group with the 966 patients in the placebo group, the authors reported no significant differences in preterm delivery, preterm delivery at less than 32 weeks, low birthweight rate, or very low birthweight rate. In addition, metronidazole treatment did not decrease the likelihood PROM, clinical intraamniotic infection, or postpartum infection (65). The disparate results of these metronidazole treatment trials have several possible explanations. There were differences in the general obstetric populations studied: Hauth et al. (66) and Morales et al. (63) limited their study to patients at very high risk for preterm birth, whereas McDonald et al. (64) and Carey et al. (65) studied lower-risk populations. In addition, Carey et al. (65) used a short-course therapy. The results suggest that in women with a previous preterm birth and BV, treatment in the second trimester for 1 week or more with oral metronidazole results in a significant reduction in the incidence of preterm delivery. There is no significant reduction in preterm delivery when antibiotics are administered vaginally or for a shorter period of time. There also is no significant reduction in low-risk women (30).

As noted in Chapter 3, heavy maternal colonization with GBS is associated with a small but statistically significant increase in LBW. However, in an accompanying randomized clinical trial, prenatal treatment with antibiotic (erythromycin given for up to 6 weeks) led to no significant improvement in birthweight, LBW, preterm birth, or

preterm PROM.

The first trial of adjunctive use of antibiotics in patients in preterm labor was conducted by McGregor and colleagues (67), who gave oral erythromycin or placebo to patients receiving tocolytics for premature labor. Although the sample sizes were extremely small, results showed a significant increase in number of days until delivery (32 vs. 22; $p = 0.02$) and delivery at 37 weeks or greater (7/8 vs. 3/9; $p = 0.035$) in the erythromycin group versus the placebo group. On the other hand, these data were selected from a larger study group. If repeated analyses were done, the likelihood of a chance observation (i.e., an error) is increased. However, the group of patients with cervical dilation is perhaps the very one in which an effect of antibiotics might be expected.

Prompted by these intriguing results, several other trials have been reported (68,69,70,71 and 72). None found that adjunctive use of antibiotics was accompanied by a decrease in perinatal mortality. The largest study of this design was a multicenter trial conducted through the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (72). As shown in Table 19.5, 275 patients were evaluated, and the results showed no measurable benefit of combination antibiotic use (ampicillin-amoxicillin plus erythromycin) compared with placebo.

Outcome	Antibiotic (N = 131)	p	Placebo (N = 144)
Delivery <37 wk	53%	NS	52%
Interval to delivery (median days)	35	NS	32
Severe newborn complications	15%	NS	15%
Birthweight (mean g)	2,535	NS	2,683
Neonatal intensive care unit stay (median days)	13	NS	11

[a]Ampicillin/amoxicillin plus erythromycin.
From Romero R, Sibai B, Cantis S, et al. Antibiotic treatment of preterm labor with intact membranes: a multicenter, randomized, double-blinded, placebo-controlled trial. Am J Obstet Gynecol 1989;160:764–774.

TABLE 19.5. NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT MATERNAL-FETAL MEDICINE UNITS NETWORK TRIAL OF ANTIBIOTICS[a] IN PRETERM LABOR WITH INTACT MEMBRANES

In a recent metaanalysis, ten studies were identified and seven, including 795 women, were evaluated. The antibiotic trials were heterogeneous with regard to the antibiotics used: three used b-lactams, two ampicillin plus erythromycin, one clindamycin, and one ampicillin plus metronidazole (73). Overall, the metaanalysis found a significant delay in delivery in only two of the seven studies. There was no significant difference in the outcomes of clinical chorioamnionitis, endometritis, or maternal infection. Regarding neonatal outcomes, there was no significant difference in neonatal death rate, neonatal sepsis, neonatal pneumonia, necrotizing enterocolitis, respiratory distress syndrome, or intraventricular hemorrhage. Two other trials used metronidazole plus ampicillin and noted a significant delay in

delivery accompanied by an increase of approximately 200 to 300 g in mean birthweight. In addition, there was a reduction in the incidence of preterm delivery and neonatal morbidity compared with placebo (74,75). The mixed findings of these studies prompted the question as to why adjunctive antibiotics in patients in preterm labor (but with intact membranes) do not consistently prevent preterm birth or neonatal morbidity associated with preterm birth. One explanation is that infection is simply not a significant cause of preterm labor, but this seems unlikely in view of all the other evidence. Another explanation is that studies individually and even in metaanalysis may have had too low a power. Further, it is likely that preterm labor has multiple causes. Thus, a true effect of antibiotics is diluted by cases of preterm labor not caused by infection. A reasonable explanation is that the antibiotics studied in most of the trials were simply the wrong ones (for example, they did not include antibiotics with better anaerobic activity) or that the antibiotics were given too late. Another interesting speculation is that bacterial lysis as a result of antibiotic therapy may lead to elaboration of lipopolysaccharide and thus enhance preterm labor itself.

The first trial of the use of antibiotics in preterm PROM was reported in 1988 (76). In the last few years, several other works of similar design have been published. Most of these reports showed a significant prolongation of pregnancy (77,78,79,80,81,82,83,84 and 85).

In 1995, a metaanalysis of antibiotic use in preterm PROM to delay delivery was reported. Of 24 trials identified, 13 were included, containing nearly 1,600 patients. Again, antibiotic trials were heterogeneous with regard to the antibiotics used; most antibiotics were b-lactams or erythromycin. No standard use of steroids, tocolytics, or GBS prophylaxis was applied (85). The overall results of this metaanalysis showed a delay in delivery of 7 days ($p = 0.07$), a reduction in chorioamnionitis ($p < 0.01$), and a reduction in confirmed neonatal sepsis ($p = 0.03$). There was no significant reduction in postpartum infection, neonatal death, neonatal pneumonia, neonatal bacteremia, respiratory distress syndrome, or necrotizing enterocolitis.

In 1997, a clinically important randomized trial on the use of antibiotics after preterm PROM was reported (86). Patients were enrolled between 24 and 32 weeks, provided rupture of the membranes had occurred less than 2 hours previously. Patients were excluded if there was chorioamnionitis, fetal distress, or labor. The antibiotic regimen consisted of ampicillin plus erythromycin given intravenously for 2 days and then orally to complete a 7-day course versus placebo. It is important to note that neither tocolytics nor steroids were used; GBS was treated when identified. The primary endpoint was a composite prospectively defined endpoint of neonatal death or RDS, grade III or IV intraventricular hemorrhage, grade II or III necrotizing enterocolitis, or neonatal sepsis. The overall results of this trial in the GBS-negative group are shown in Fig. 19.7, Fig. 19.8 and Fig. 19.9. A summary of the benefits is given in Table 19.6.

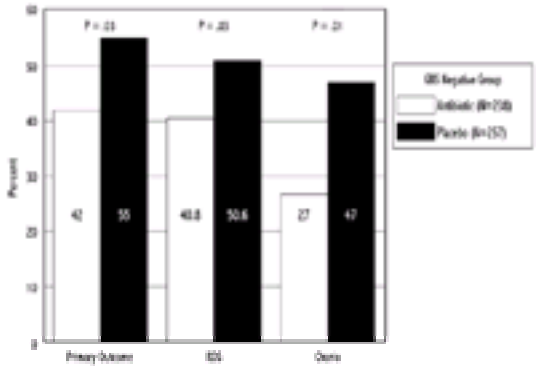


FIGURE 19.7. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial of antibiotics after preterm premature rupture of the membranes for primary outcome, respiratory distress syndrome, and chorioamnionitis.

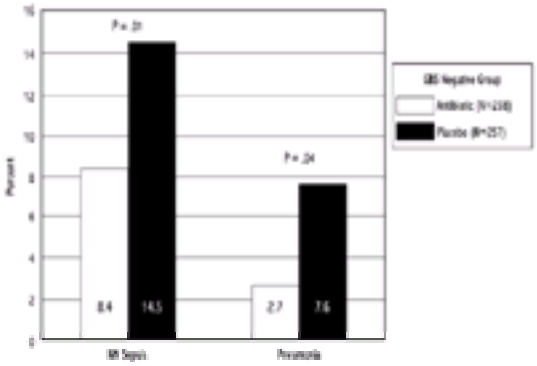


FIGURE 19.8. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial of antibiotics after preterm premature rupture of the membranes for neonatal sepsis and neonatal pneumonia.

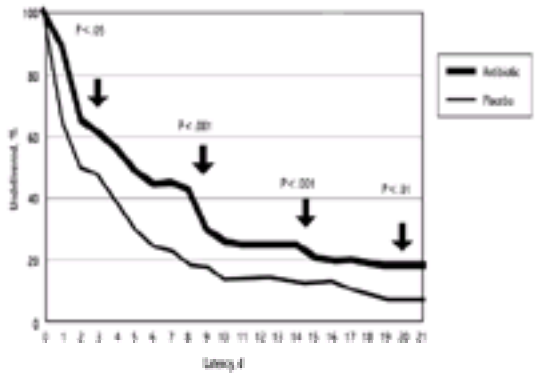


FIGURE 19.9. Prolongation of pregnancy in the group B streptococcus-negative

cohort.

	Total Population	Group B Streptococcus-Negative Cohort
Primary outcome	↓↓ (p = 0.04)	↓↓ (p = 0.03)
Respiratory distress syndrome	↓↓ (p = 0.04)	↓↓ (p = 0.03)
Necrotizing enterocolitis	↓↓ (p = 0.03)	
Amnionitis	↓↓ (p = 0.01)	↓↓ (p = 0.01)
Neonatal sepsis		↓↓ (p = 0.01)
Neonatal pneumonia		↓↓ (p = 0.04)

From Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes: a randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA 1997;278:989–995.

TABLE 19.6. BENEFITS OF THE MATERNAL-FETAL MEDICINE UNITS NETWORK TRIAL

Empiric use of antibiotics to prevent prematurity has resulted in serious infections with resistant organisms in the mother and infant (87) and a significant increase in neonatal necrotizing enterocolitis (83). These consequences should caution us on our use of antibiotics as panaceas. Our recommendations are summarized in Box 19.1, Box 19.2, Box 19.3.

Thus, during prenatal care, antibiotics should be used to prevent preterm birth by treating bacteriuria and infection with *N. gonorrhoeae* and *C. trachomatis,* and in high-risk patients with BV. On the other hand, ureaplasmas or GBS genital colonization should not be treated. Group B streptococcus prophylaxis is indicated in patients who have preterm labor with intact membranes, but routinely giving antibiotics to prevent preterm birth is not established. Although not a standard, it may be reasonable to treat BV in such patients. Finally, in patients who have preterm PROM, broad-spectrum combination antibiotic therapy prolongs pregnancy and lowers neonatal morbidity. One such regimen is ampicillin and erythromycin given intravenously for the first 2 days and then orally for the remaining 5 days. Group B streptococcus prophylaxis should be given to patients with preterm PROM when patients go into labor, according to the Centers for Disease Control and Prevention guidelines. See Chapter 3 for discussion of GBS management.

Box 1

Use of Antibiotics During Prenatal Care to Prevent Preterm birth

- Treat bacteriuria
- Treat *N. gonorrhoeae*
- Treat *C. trachomatis*
- Treat BV in high-risk patients (defined, for example, as those with previous preterm birth or previous preterm PROM).
- Do not treat *U. urealyticum* or GBS genital colonization

Box 2

Use of Antibiotics in Preterm Labor with Intact Membranes to Prevent Preterm birth

- Do not give antibiotics routinely to prevent PTB.*
- Although not standard, it may be reasonable to treat BV. Optimal dose and duration are not established.

*GBS prophylaxis is indicated.

Box 3

Use of Antibiotics with PROM to Prevent Preterm birth

- At 24 to 32 weeks, give broad-spectrum antibiotics such as ampicillin plus erythromycin for 7 days.
- Other regimens also may be effective.

*GBS prophylaxis should be indicated.

In summary, a large body of clinical and laboratory information suggests that subclinical infection is a cause of preterm birth. This concept holds promise that new approaches can be developed to prevent prematurity.

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20

POSTPARTUM INFECTION

Seven decades into the antibiotic era, genital tract infections continue to pose a common and occasionally severe threat to women after childbirth. Although substantial progress has been made in the control of puerperal sepsis, infection still ranks as the fourth most common cause of maternal death (1).

Epidemiology

Older studies had reported the incidence of "standard puerperal morbidity," which was defined by the U.S. Joint Committee on Maternal Welfare as "a temperature of 100.4°F (38.0°C), the temperature to occur in any two of the first 10 days postpartum, exclusive of the first 24 hours, and to be taken by mouth by a standard technique at least four times daily." Yet the full criteria of the original definition can no longer be applied because of early patient discharge practices. In addition, many infected patients respond to antibiotics so quickly that they do not meet the temperature criteria for standard morbidity.

Low-grade fever (³100.4°F) or isolated higher temperature elevations occur commonly in the puerperium and often resolve spontaneously, especially after vaginal delivery (2). In a study of 1,000 consecutive gravidas, Filker and Monif (2) noted that 6.5% (65) of patients developed a temperature greater than 38°C (100.4°F) within the first 24 hours. Half of these patients delivered vaginally and accounted for 3.8% of all vaginal deliveries. Eighty percent (26) of these 33 patients resolved the fever spontaneously. The other 32 patients were delivered by cesarean section and accounted for 22.5% of all abdominal deliveries. In this group, the fever resolved spontaneously in only 30% (8). The etiology of such fevers is unclear. Recent data from our laboratory suggest that these transient fevers often are due to transient bacterial infection in the uterus, as detected by positive amniotic fluid cultures (3). Sources of infection in the puerperal period are genital tract infection

(endometritis, septic pelvic thrombophlebitis, and abscess), urinary tract infection, mastitis, breast abscess, and complications of anesthesia.

At present, the overall rate of postpartum uterine infection may be estimated at 1% to 2% after vaginal delivery and up to 27% after cesarean delivery, even when prophylactic antibodies are used (3). Although the absolute risk of death from infection is small among postpartum women, sepsis remains a common cause of maternal death in the United States. In the period 1987 to 1990, infection accounted for 12% (96/797) of deaths after livebirth in the United States. Infection ranked behind hypertensive disorders (24%), embolism (23%), and hemorrhage (21%). Ranking after infection were cardiomyopathy (6%) and anesthesia (3%) (1). In terms of pregnancy-related mortality for the same period, the rate was approximately 1.4 per 100,000 liveborns in the United States (Fig. 20.1 and Fig. 20.2).

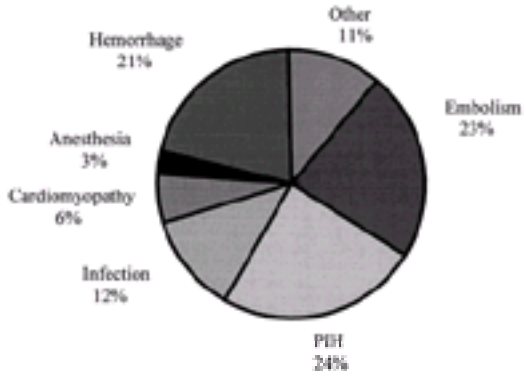


FIGURE 20.1. Causes of pregnancy-related death. Adapted from ref. 1.

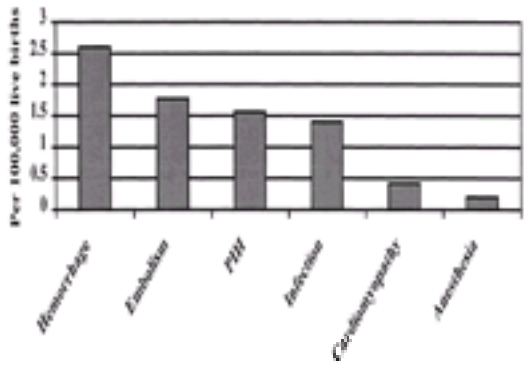


FIGURE 20.2. Pregnancy-related mortality. Adapted from ref. 1.

Older studies had indicated that the deaths were preventable in more than two thirds of the cases, with both patient and medical personnel sharing responsibility equally. Patient responsibility consisted primarily of delay in seeking medical care (for

example, after prolonged rupture of the membranes [PROM]); physician and hospital responsibility consisted of inadequate evaluation of symptoms, incorrect diagnosis, failure to hospitalize earlier, and inadequate institution of antibiotic therapy.

Epidemic infections occur infrequently on maternity services. Lethal outbreaks of b-hemolytic streptococcal infection occurred as late as 1927, and a number of nonlethal epidemics of streptococcal infection have been reported since 1965. These epidemics were all caused by group A streptococci (usually of one type) and involved from 2 to 20 mothers, 0 to 11 newborn infants, and many of the hospital staff. Although there were no maternal or neonatal deaths, a number of the patients were severely ill (4). There have been no reported epidemics of puerperal infection due to organisms other than group A streptococci.

Genital Tract Infection

The most common cause of puerperal fever is uterine infection; the infection is variously called endometritis, endoparametritis, or simply metritis. Criteria for endomyometritis include fever, uterine tenderness, purulent or foul lochia, peripheral leukocytosis, and exclusion of another infected site. Nonspecific signs and symptoms, such as malaise, abdominal pain, chills, and tachycardia, may be present. However, most patients do not have this complete clinical picture. Many febrile patients with group A or B streptococcal bacteremia have no localizing signs early in the course of the illness (5). In the vast majority of cases of uterine infection, presenting signs and symptoms develop within the first 5 days after delivery.

When endometritis is suspected, we suggest that an aerobic cervical culture be performed. (There currently is no available technique to obtain an endometrial specimen free of cervical contamination.) Even though broad-spectrum therapy is used, this culture may identify pathogens that require specific therapy. For example, identification of group A streptococcus should lead to isolation of the patient and should be reported to physicians in the nursery. Isolation of group B streptococcus (GBS) or *Neisseria gonorrhoeae* should be reported to physicians in the nursery. In addition, there may be isolates that will help direct subsequent antibiotic therapy in case of initial antibiotic failure. Examples include enterococci in initial therapy with a cephalosporin or clindamycin plus gentamicin. Then, from a surveillance viewpoint, it is necessary to determine whether kinds of organisms or their antimicrobial susceptibilities are shifting. Results of these cultures at a given institution also allow for development of specific antibiotic strategies. The commonly used algorithm of not performing a pelvic examination, not performing cultures of the pelvis, and empirically prescribing antibiotics in patients with postpartum infection is to be decried. As recently noted by Soper (6), this empiricism “will lead to a generation of specialists in women's health who fail to appreciate a logical approach to the evaluation of women with fever and/or infections. It leads not only to empiric diagnosis, but empiric therapy, without the opportunity to document disease. It allows for no future planning in case of emerging resistant organisms.”

About 10% to 20% of patients with endometritis have bacteremia, and blood cultures should be obtained for women with puerperal fever. Isolation of an organism from the blood does not imply that this organism, by itself, is responsible for the infection; therefore, antibiotic therapy directed solely against the isolate thus identified might be inadequate.

Pathophysiology: Risk Factors

Method of Delivery

Cesarean section is the major predisposing clinical risk factor for pelvic infection (Table 20.1) (7). After abdominal delivery, the frequency and severity of infection are greater than after vaginal delivery. In a recent report, endometritis occurred in 1.2% after vaginal delivery and in 27% after cesarean delivery, even though prophylactic antibiotics were used routinely (3).

Duration of labor
Cesarean delivery, especially nonelective
Nonelective cesarean delivery without prophylactic antibiotics
Duration of rupture of membranes
Failure to progress in labor
Number of vaginal examinations
Duration of internal fetal monitoring
Low socioeconomic status
Diabetes

TABLE 20.1. MAJOR RISK FACTORS FOR POSTPARTUM INFECTION IN RECENT STUDIES

The severity of infection is increased in abdominal delivery. Antibiotic failure rates and complication rates are higher for the cesarean section group (8,9). Serious complications such as abscess or presumed septic pelvic thrombophlebitis have been reported in 2% to 4% of patients with endometritis after cesarean section (8). With broader antibiotic therapy aimed at the anaerobes, however, these complications appear to be less common (10). Death from sepsis is undeniably increased after cesarean section (7). In absolute terms, the death rate from sepsis was one per 1,600 cesarean sections. Sepsis may be less of a threat at other institutions; one series of 10,000 consecutive cesarean sections at a level III hospital reported not a single maternal death from any cause (11).

The increased incidence of infection in cesarean section probably is due to increased intrauterine manipulation, foreign body (suture), tissue necrosis at the suture line, hematomaseroma formation, and wound infections. Several studies noted that women who develop postpartum endometritis commonly have positive cultures of the amniotic fluid at the time of section (12,13 and 14).

Clearly, not all patients undergoing cesarean section are at equal risk. Patients with electively scheduled operations (with no labor and no rupture of the membranes [ROM]) have lower infection rates than those with emergency or nonelective procedures (with labor, ROM, or both). This observation was made nearly universally

in a large number of studies (Table 20.1).

Labor, Rupture of Membranes, Vaginal Examinations, and Internal Fetal Monitoring

These risk factors are intricately interrelated, and even sophisticated statistical techniques may not be able to discern which of these factors is the independent variable (15). Several studies have identified that, after correcting for confounding variables, the duration of labor was most significant (7,16). Others have shown that with passage of time and after ROM, bacterial contamination of the amniotic cavity occurs (12,13,17). After eliminating confounding variables with a discriminant analysis technique, D'Angelo and Sokol (18) reported that the most significant event related to postpartum morbidity after cesarean section was the duration of labor. Other studies using similar statistical techniques confirmed this result (7).

Whether amniotomy increases postpartum infection has been the subject of many reports. Garite (19) concluded that amniotomy, as part of a plan of active labor management, did not increase the risk. This conclusion was based on six randomized controlled trials of amniotomy (19). Among patients with arrest of labor, Rouse and colleagues (20) found that maternal infection (the sum of clinical chorioamnionitis and endometritis) was increased in patients randomized to both amniotomy and oxytocin compared with patients with oxytocin alone.

Newton and coworkers (21) performed a large multifactorial study of AF colonization and clinical factors as predictors of postpartum endometritis. By logistic regression, they found that once they accounted for bacteria present in the AF during labor, most “traditional” risk factors were no longer significant. (The sole exception was cesarean delivery, which remained a significant risk factor.) The authors hypothesized that risk factors such as long labor, PROM, vaginal examinations, and internal monitoring serve to facilitate bacterial ascent into the amniotic cavity. Once the analysis accounts for this bacterial invasion, then nearly all of the clinical risk factors (except cesarean delivery) drop out as risk factors (21). Vaginal examinations carry no greater infection risk than do rectal examinations in labor. In some studies, the number of vaginal examinations correlated with risk of infection, but in many other studies, this clinical variable was not identified as a risk factor. Because the internal fetal monitor (IFM) is a foreign body, there has been concern that its use may increase intrauterine infection. However, it is difficult to separate the effect of IFMs, because they often are used in patients with abnormal labor, prolonged ROM, and cesarean delivery and thus already at increased risk for infection. Although some studies have implicated internal monitoring as a risk factor (22,23), other studies show no direct increase in infection with IFM (24,25).

Socioeconomic Status

Regardless of race, indigent patients have higher rates of puerperal infection than do middle-class patients. The cause is unclear, but differences in flora, hygiene, and nutrition have all been postulated as reasons.

Other Factors

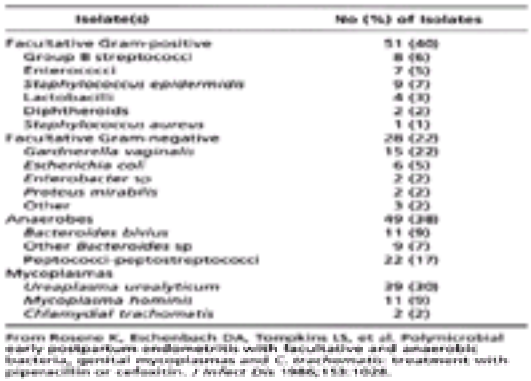
Anemia has been associated with postpartum infection in several studies. Anemia

may simply represent a marker for poor nutrition or lower socioeconomic class. Obesity has not been a consistent risk factor for genital infection, but it has been a risk factor for wound infection in general surgery. Among obese women undergoing cesarean section, increased surgical duration and operative blood loss increased the risk of surgical morbidity (wound infection or endometritis) (26). Minkoff et al. (27) found that maternal colonization with GBS correlated with puerperal infection. Chestnut et al. (28,29) reported that in both primary and repeat cesarean sections, general anesthesia does not increase the risk of infectious morbidity. Diabetes also is a risk factor for endometritis. Among patients without labor or ruptured membranes, 9.1% (5/55) of diabetics developed endometritis or wound infection versus 1.8% (2/110) of nondiabetics (p = 0.042). Among patients with labor, ROM, or both, the infection rate for diabetics was 25% (6/24) versus 6.3% (3/48) for nondiabetics (p = 0.032) (30).

Microbiology

Endometritis most often seems to be a mixed infection with aerobic and anaerobic bacteria from the genital tract (31). On average, two to three microbial isolates can be recovered from the endometrial cavity, but six to seven may be isolated in some patients. In a study of 198 patients with endometritis after cesarean section, 53.5% of the endometrial isolates were aerobes and 46.5% were anaerobes (32).

In 1986, Rosene and coworkers (33) reported detailed endometrial and blood culture results for 55 women with carefully defined postpartum endometritis (fever, abdominal pain and tenderness, and no other source of fever). Patients who received prophylactic antibiotics were excluded. Endometrial cultures were obtained via a triple-lumen catheter for aerobes, anaerobes, genital mycoplasmas, and *Chlamydia trachomatis.* Blood cultures were performed for genital mycoplasmas and bacteria. Of 53 cases, 51 (93%) had one or more organisms. Multiple species were recovered in 69%; two or more bacterial species, together with genital mycoplasmas, were present in 57%. *Chlamydia trachomatis* was isolated in 4% (Table 20.2).



Isolate(s)	No (%) of Isolates
Facultative Gram-positive	51 (40)
Group B streptococci	8 (6)
Enterococci	7 (5)
Staphylococcus epidermidis	9 (7)
Lactobacilli	4 (3)
Diphtheroids	2 (2)
Staphylococcus aureus	1 (1)
Facultative Gram-negative	28 (22)
Gardnerella vaginalis	15 (22)
Escherichia coli	6 (5)
Enterobacter sp	2 (2)
Proteus mirabilis	2 (2)
Other	3 (2)
Anaerobes	49 (38)
Bacteroides bivius	11 (9)
Other Bacteroides sp	9 (7)
Peptococci-peptostreptococci	22 (17)
Mycoplasmas	
Ureaplasma urealyticum	39 (30)
Mycoplasma hominis	11 (9)
Chlamydial trachomatis	2 (2)

From Rosene K, Eschenbach DA, Tompkins LS, et al. Polymicrobial early postpartum endometritis with facultative and anaerobic bacteria, genital mycoplasmas and C. trachomatis: treatment with piperacillin or cefoxitin. J Infect Dis 1986;153:1024.

TABLE 20.2. ENDOMETRIAL ISOLATES (COLLECTED BY A TRIPLE-LUMEN CATHETER) FROM 51 PATIENTS WITH POSTPARTUM ENDOMETRITIS

Aerobic or facultative organisms are found in approximately 70% of genital cultures. The Gram-negative bacilli, *Escherichia coli* and *Gardnerella vaginalis,* are most common (found in up to 30% of patients). Gram-positive aerobes are recovered commonly; the streptococci are the most frequent pathogenic isolates. Group B streptococci are isolated in about 15% of genital isolates from patients with endometritis. *Neisseria gonorrhoeae* may be found rarely, usually as part of a mixed infection.

Special management is required for certain aerobic microorganisms. Identification of GBS is important, because the neonate may be colonized and at risk for fulminant sepsis. The nursery should be notified whenever GBS is isolated in a mother. Likewise, group A streptococcal infections must be regarded with special concern, as an epidemic may develop from a point source. The patient with a group A streptococcal infection should be isolated to avoid spread. During the past few years, there has been a noteworthy increase in virulence of group A streptococci in nonobstetric as well as obstetric patients. Case series from Texas and Colorado have described fulminant, life-threatening puerperal infections due to group A streptococci (34). Cases are marked by bacteremia, shock, and multiorgan involvement (Table 20.3). Commonly, there is poor response to vigorous medical and antibiotic therapy, often with the need for hysterectomy to save the patient's life (Fig. 20.3). *Staphylococcus aureus* is another important offender because of its resistance to penicillin and its propensity for metastatic infection; however, this organism occurs in less than approximately 5% of genital infections.

	Case No.		
	1*	2*	3
Clinical Feature			
Underlying disease	No	No	No
Vaginal delivery	Yes	Yes	Yes
Onset (days)	7	2	4
Temperature (°C)	39.6	40.2	38.2
Complication			
Shock	Yes	Yes	Yes
Bacteremia	Yes	Yes	Yes
Disseminated intravascular coagulation	Yes	Yes	Yes
Adult respiratory distress syndrome	Yes	Yes	No
Renal insufficiency	Yes	Yes	Yes
Hepatic dysfunction	Yes	Yes	Yes

*Data from Silver RM, Heddleston LN, McGregor JA, et al. Life threatening puerperal infection due to group A streptococci. Obstet Gynecol 1992;79:894–896.

TABLE 20.3. GROUP A STREPTOCOCCAL PUERPERAL SEPSIS IN COLORADO, 1989–1991

FIGURE 20.3. Laparotomy in a case of group A streptococcal puerperal sepsis. Over 2,500 mL of purulent peritoneal fluid were drained and hysterectomy was necessary.

Anaerobic organisms clearly have major roles in postpartum infection and are found in 40% to 60% of properly collected and handled cultures. The most common isolate often is a member of the *Bacteroides/Prevotella* sp. These Gram-negative bacilli are important because of their role in intraperitoneal abscess formation and their pattern of resistance to antibiotics. Although much attention in the last decade has been directed to *Bacteroides fragilis,* a number of hospitals throughout the United States report *Prevotella bivia* (formerly *Bacteroides bivius*) as the predominant anaerobic isolate from the genital tract. Both of these microorganisms are resistant to many antibiotics, such as penicillin. Clindamycin, chloramphenicol, metronidazole, and some of the newer penicillins and cephalosporins have good activity against these species. Other common anaerobic isolates are the anaerobic streptococci (*Peptococcus* sp and *Peptostreptococcus* sp), *Fusobacterium* sp, and *Clostridium* sp. These organisms usually are sensitive to many commonly used antibiotics, including penicillin and clindamycin. Most patients with *Clostridium perfringens* infection (even bacteremia) do well with antibiotic therapy alone. Thus, isolation of *C. perfringens,* even from the bloodstream, should not by itself prompt surgical intervention. Hysterectomy should be reserved for cases with evidence of myonecrosis.

Genital mycoplasmas (*Mycoplasma hominis* and *Ureaplasma urealyticum*) are most likely involved in the microbial pathogenesis of postpartum infection. These organisms have been recovered from the bloodstream of patients with postpartum fever. In addition, these organisms, when isolated from the chorioamnion of patients having cesarean section, have been significantly associated with postpartum endometritis (33,35,36 and 37). Platt and coworkers (38) reported an association between a fourfold rise in mycoplasmacidal antibody titer and fever after vaginal delivery. However, many patients with puerperal infection respond to antibiotics not active against the genital mycoplasmas (see Chapter 4).

There is some evidence that *C. trachomatis* may be involved in a late-onset, mild endometritis after vaginal delivery (39). In a study of early postpartum endometritis (the vast majority of which occurred after cesarean delivery), Watts et al. (40) collected endometrial samples using a triple-lumen catheter and found *C. trachomatis* in only 2.5% (4/150). There was a good clinical response in all patients

with *C. trachomatis,* but the organism was reisolated from four of nine patients for whom follow-up cultures were available. (This suggests the possibility that silent chlamydial infection in the upper genital tract may cause infertility). The prevalence of *C. trachomatis* in the endometrium in this study was similar to that in the antenatal population, and all patients with *C. trachomatis* in the endometrium had other isolates that could have accounted for the endometritis. Thus, the authors concluded that there is only limited evidence that *C. trachomatis* causes early endometritis.

Diagnosis

The diagnosis of endomyometritis usually is based on symptoms of fever, malaise, abdominal pain, and purulent or foul lochia. Other sources of fever should be excluded. In clinical investigations, various temperature criteria, including 100°F (37.8°C) and 100.4°F (38°C) on usually two or more occasions, have been used in the definition of endometritis. When there are signs of infection, multiple risk factors for infection, or persistence of low-grade fever in the puerperium, it is reasonable to presume a genital tract infection is present and proceed with the workup and treatment. We believe that appropriate specimens include a complete blood count, blood cultures, and an aerobic uterine culture. Gram staining of the genital specimen may be helpful when hemolytic streptococci, clostridia, or other anaerobes are suspected.

Treatment

With supportive therapy and appropriate antibiotics, the vast majority of patients improve within 1 to 3 days. Among patients with endomyometritis after vaginal delivery, responses to “older” therapy with penicillin plus an aminoglycoside has been close to 95%, even though this combination has a limited anaerobic spectrum (8). In patients with poor responses, addition of appropriate antibiotics resulted in an overall culture rate of 98%. Examples of appropriate additional antibiotics include clindamycin or metronidazole for a presumed anaerobic infection. Given the wide choice of safe effective antibiotics, the regimen used to treat endometritis after vaginal delivery should include good anaerobic coverage, probably using a single agent (such as a broad-spectrum penicillin or cephalosporin or a penicillin–b-lactamase inhibitor combination).

Among patients with endomyometritis after cesarean section, response to antibiotics is poorer. Prospective studies have found a cure rate of 65% to 78% in response to therapy with poor anaerobic activity, such as penicillin plus aminoglycoside and penicillin plus tetracycline (9,10,41). In about half of the failures, the cause can be identified and includes a resistant organism (often *B. fragilis* when penicillin plus aminoglycoside is used), wound infection, pelvic hematoma or abscess, and presumed septic pelvic thrombophlebitis. As with infection after vaginal delivery, the cause of apparent failure may be infection of another site or a noninfectious source.

When initial therapy consists of clindamycin plus gentamicin, the response rate of endomyometritis after cesarean section is high, and major infectious complications may be reduced (10,32). Of the genital flora, the enterococcus is the only common isolate that is resistant to this combination.

Initial therapy for endometritis after cesarean section should consist of

broad-spectrum antibiotics with activity against all the anaerobes as well as Gram-positive and Gram-negative aerobes. Ampicillin, penicillin-gentamicin, ampicillin-gentamicin, and cephalothin-gentamicin do not provide this spectrum. In many clinical trials, the combination of clindamycin and aminoglycoside has been considered the standard for comparison for treatment of genital tract infections after cesarean section. Considerations in use of the clindamycin-gentamicin regimen are several. First, in some trials, the failure rate has been higher (up to 20%–25%) (42), perhaps because of the emergence of enterococcus as a pathogen when cephalosporin prophylaxis is used. In addition, both clindamycin and gentamicin have potentially serious side effects. Clindamycin therapy may lead to diarrhea in 2% to 6% of patients and rarely to pseudomembranous colitis. Aminoglycoside therapy may lead to nephrotoxicity or ototoxicity, and “therapeutic” aminoglycoside levels may be difficult to achieve in obstetric patients with standard dosing regimens. Third, the administration of two drugs is more time consuming and expensive than single-agent therapy, but clindamycin may be administered at 900 mg intravenously every hour and safely admixed with gentamicin for intravenous infusion.

A large number of new penicillins and cephalosporins to treat postpartum infection have become available. Although no single agent provides activity against the entire bacterial spectrum, most have sufficient aerobic and anaerobic activity to merit use in endometritis (see Chapter 23 for a more complete discussion). Specific regimens are listed in Table 20.4.

Regimen	Organisms "Resistant" to the Regimen	Comments
Clindamycin plus gentamicin	Mainly enterococci	Often a standard for comparison
Cefoxitin, cefotetan, or alternative cephalosporin-like antibiotics	Mainly enterococci	Avoid in cases of immediate hypersensitivity to penicillin
Ampicillin-sulbactam (Unasyn)		Contraindicated in cases of penicillin allergy
Ticarcillin-clavulanic acid (Timentin)	Some aerobic Gram-negative rods	
Piperacillin-tazobactam (Zosyn)	Some aerobic, Gram-negative rods, some Staphylococcus aureus	
Piperacillin, mezlocillin, or other ureido penicillins		Contraindicated in case of penicillin allergy
Clindamycin plus aztreonam	Mainly enterococci	Alternative to gentamicin plus clindamycin
Metronidazole plus gentamicin	Group B streptococci, enterococci, and other aerobic streptococci	Absence of streptococcal activity limits its role in endometritis
Imipenem/cilastatin, meropenem, and other carbapenems	Some clostridia, some E. aureus	Because of unusual spectrum of activity, reserve for treating difficult infections

TABLE 20.4. SELECTED REGIMENS FOR INITIAL PARENTERAL THERAPY OF POSTPARTUM ENDOMETRITIS

The new penicillins and cephalosporins usually are very well tolerated and have few side effects. Also, therapeutic serum levels can be achieved easily without much concern with dosing. Administration of a single agent requires less time and equipment, but the higher cost of most newer agents must be considered.

Metronidazole has excellent anaerobic activity. Because it has little activity against aerobes, its use as single-agent therapy is generally unwise. Its use in combination with gentamicin still leaves the Gram-positive aerobes (notably GBS and *Enterococcus*) uncovered.

New antibiotics are being formulated that may replace gentamicin as initial therapy. The monobactams (e.g., aztreonam) have exquisite Gram-negative activity, but they have little activity in the rest of the bacterial spectrum. These agents have the same spectrum as the aminoglycosides and should have fewer potential side effects. Clinical trials of these monobactams in combination with clindamycin have shown excellent results, equivalent to clindamycin plus gentamicin.

For patients who respond promptly to parenteral antibiotics, some questions arise: How long should therapy be continued? Is oral therapy needed as an adjunct?

It has been recommended that parenteral therapy should be continued for 24 to 48 hours after the patient becomes “completely afebrile and asymptomatic” (31). Intravenous antibiotics then may be discontinued and the patient discharged without oral antibiotics, unless the patient has had staphylococcal bacteremia (31). Three descriptive reports have supported the appropriateness of this approach. Cabbad and colleagues (43) reported that among 25 indigent patients, intravenous therapy with imipenem was continued for 24 to 36 hours after defervescence (temperature threshold for fever was not specified). No oral antibiotics were used, and all patients remained well. Soper et al. (44) continued intravenous gentamicin plus clindamycin until the patient's temperature was 99.5°F or less for 24 hours; no oral antibiotics were prescribed. Only two (4%) of 54 patients required readmission (one with “viral gastroenteritis” and one with endometritis and retained placental tissue). Similarly, Stovall et al. (45) continued parenteral antibiotic therapy (clindamycin plus gentamicin) until the temperature was less than 99.5°F for 12 to 24 hours and until there was no evidence of pelvic abscess or uterine tenderness. Antibiotics then were discontinued and the patient discharged. Of 106 patients, only two were readmitted, both with superficial wound separations; there were no infectious complications (45).

The conclusions of these descriptive studies are supported further by a randomized trial of oral antibiotic therapy after successful intravenous therapy in women with puerperal endometritis. In San Antonio, Dinsmoor and coworkers (46) showed that patients given placebo had similar subsequent courses to those of patients given oral amoxicillin (after parenteral therapy). Side effects were similar in both groups (Table 20.5).

Variable	Placebo (N = 49)	Amoxicillin (N = 50)
Recurrent endometritis	0	0
Wound infection	0	0
Side effects		
Any	14%	10%
Stopped medications	2%	4%
Completed medication (5 days)	65%	52%

[a]Cefoxitin, clindamycin-gentamicin, or ampicillin-sulbactam.
From Dinsmoor MJ, Newton ER, Gibbs RS. A randomized, double-blind, placebo-controlled trial of oral antibiotic therapy following intravenous antibiotic therapy for postpartum endometritis. *Obstet Gynecol* 1991;77:60–62.

TABLE 20.5. ORAL AMOXICILLIN AFTER INTRAVENOUS ANTIBIOTICS[a] FOR

POSTPARTUM ENDOMETRITIS

At the other end of the patient response spectrum are patients who do not respond within 48 to 74 hours of appropriate antibiotic therapy. Diagnostic considerations are (a) an infected “mass,” such as abscess or hematoma of the wound or pelvis, extensive pelvic cellulitis, septic pelvic thrombophlebitis, or retained placenta; (b) a resistant organism, such as enterococcus, in patients treated with cephalosporin-like antibiotics or with clindamycin plus gentamicin; (c) a nongenital source of infection, such as pyelonephritis, pneumonia, or intravenous catheter phlebitis; (d) a noninfectious fever, such as drug fever or factitial fever; or (e) inadequate dose or inadequate route of otherwise correct antibiotics (Fig. 20.4). Appropriate bedside examination and review of the chart and cultures often reveal the cause. In general, in patients who are stable and not seriously ill, an appropriate change in antibiotics (such as adding penicillin to clindamycin plus gentamicin to add coverage for enterococcus) is effective in about 80% of patients who did not respond in the initial 48 hours.

FIGURE 20.4. Causes of poor response to antibiotics.

In about 20% of cases, the initial failure to respond is due to resistant organisms; in another 30%, no cause for the failure is identified. Perhaps these “failures” simply represent not allowing sufficient time for the antibiotics to be effective. Nevertheless, we believe that 48 to 72 hours is an appropriate point to change therapy unless the patient is unstable, when changes are needed more promptly. In the remaining 40% to 50%, the reason for poor response to initial therapy is an infected mass. If the mass or collection is present in the wound after cesarean section, physical examination usually identifies the sources. In other cases, radiographic studies are helpful in identifying pelvic masses or deep-seated wound infection.

Ultrasound findings may reveal a mass in the pelvis. Faustin et al. (47) reported on 100 consecutive patients who had abdominal ultrasound examinations on the fourth to fifth day after cesarean section. Twenty-fine patients had echo-free areas detected between the anterior uterine wall and behind the bladder. Eight of these areas

measured 3.5 cm or greater. Echo-free areas (most often representing hematomas) were not associated with labor duration or length of ROM, but were associated with estimated blood loss greater than 1,000 mL (27.6% with vs. 9.9% without echo-free areas), need for transfusion (34.6% with vs. 18.8% without), and surgery longer than 90 minutes (34.5% with vs. 8.4% without). Patients with echo-free areas larger than 3.5 cm were more likely to develop standard fever and require therapeutic antibiotics. Acholonu et al. (48) reported use of percutaneous drainage of the fluid collections in seven febrile patients after cesarean section. Drainage, with continued antibiotics, was followed by resolution of fever in most patients.

In patients with persistent pelvic infection after vaginal delivery, an ultrasound examination is helpful because it may reveal a pelvic mass (Fig. 20.5), retained placental tissue, or septic pelvic thrombophlebitis (49). Sonography is readily available, is inexpensive, and requires no special preparation. When patients are obese or have an open wound, ultrasonography provides a limited examination. Brown et al. (50) found computerized tomography to be useful in diagnosing puerperal thrombophlebitis, but less useful in detecting pelvic cellulitis or abscess. In 1991, Lev-Toaff and coworkers (51) reported a retrospective series of 31 patients with persistent puerperal fever in whom diagnostic imaging studies (ultrasound and/or computerized tomographic scan or magnetic resonance imaging) were performed. Two patients had completely negative studies; in the other patients, pertinent diagnoses were suggested, including hematoma in 11, abscess in 7, and ovarian vein thrombosis in 2 (Fig. 20.6).

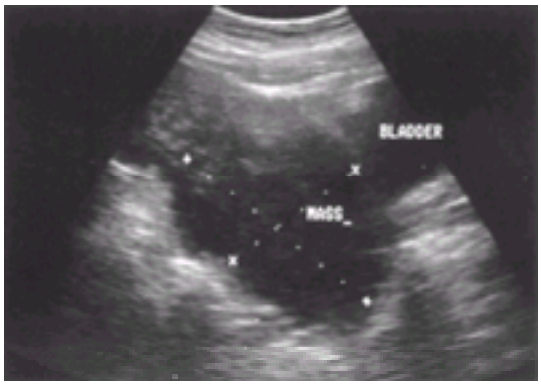


FIGURE 20.5. Longitudinal scan demonstrating an 8 × 5-cm mass lateral to the uterus in a patient with persistent fever after vaginal delivery.

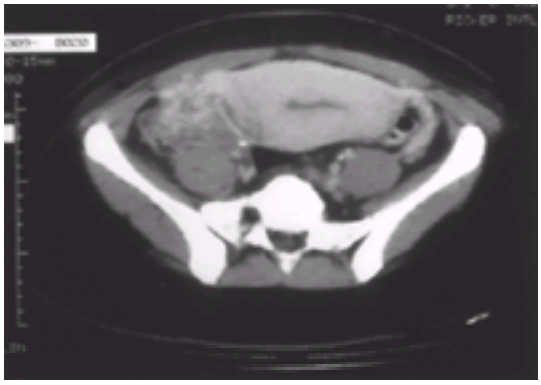


FIGURE 20.6. Computerized tomographic scan in a patient with persistent fever after cesarean delivery. Note the asymmetric “moth-eaten” mass adjacent to uterus (on **left** in scan) and anterior to psoas muscle. This was consistent with an infected hematoma.

Radiographic studies may direct subsequent therapy. As shown in Fig. 20.7, ultrasound examination showed an intrauterine collection. This led to a dilation and curettage that resulted in drainage of purulent material. As another example (Fig. 20.8), a pigtail catheter was inserted under ultrasound guidance to drain a pelvic abscess following cesarean section.

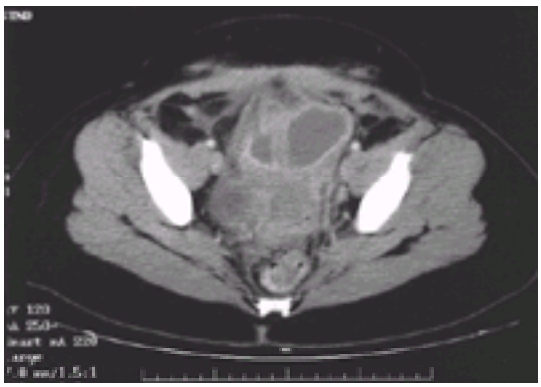


FIGURE 20.7. Parauterine abscess in a patient after cesarean delivery.

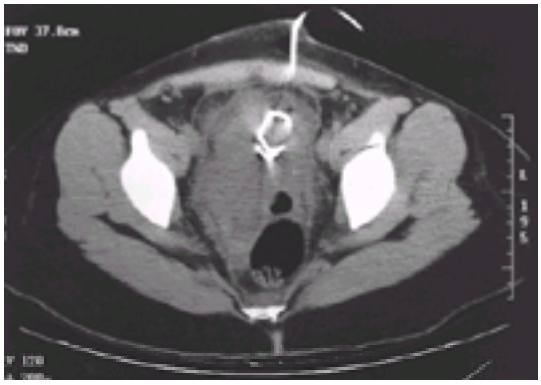


FIGURE 20.8. Computerized tomographic scan showing percutaneous placement of a pigtail catheter in an abscess after cesarean section (same case as shown in Fig. 20.7).

There has been little assessment of ambulatory therapy for postpartum infection. It is the practice of our service at the University of Colorado to initiate treatment of endometritis with intravenous antibiotic on an inpatient basis after cesarean section. Thus, if a patient returns with late pelvic infection after cesarean section, the patient is readmitted. We prefer to initiate treatment of most cases of endometritis after vaginal delivery as an inpatient with parenteral therapy. In mild cases of endometritis after vaginal delivery, therapy by the oral route occasionally has been initiated for outpatients.

Prevention

Principles for use of antibiotic prophylaxis to prevent endometritis after cesarean delivery are well established (see Chapter 24). A persistent number of women still develop infection despite prophylaxis. These prophylaxis failures are caused by invasion of the myometrial layer by bacteria (52) or by the presence of certain organisms in the upper genital tract (53). Watts et al. (53) found that the presence of *Enterococcus* sp ($p = 0.03$) and GBS ($p < 0.001$) was significantly associated with failure of cephalosporin prophylaxis. The explanation for the failures associated with isolation of enterococci probably lies in their resistance, whereas the failures associated with GBS (susceptible to the cephalosporins) may be due to other virulence factors.

Endometritis can be reduced by early recognition and early treatment of abnormal labor. In the vast experience in Dublin with “active management of labor,” there was a very low rate of chorioamnionitis and endometritis. In a randomized controlled trial of several features of active management, López-Zeno and coworkers (54) demonstrated that early recognition of arrest disorders of labor, coupled with early institution of oxytocin, resulted in major benefits, including shorter labors, lower cesarean section rates (10.5% vs. 14.1%; $p < 0.05$ by logistic regression), and less maternal infection (6.9% vs. 14.4%).

Mastitis

Both *epidemic* and *endemic* forms of puerperal mastitis may occur. *Epidemic* puerperal mastitis has occurred among hospitalized women in conjunction with staphylococcal nursery epidemics. This form of the disease has been described mainly as a mammary adenitis, involving mainly the lactiferous glands and ducts. *Endemic* puerperal mastitis occurs sporadically among nonhospitalized nursing women. This type often presents as a lobular, V-shaped cellulitis of the periglandular connective tissue (Fig. 20.9). Often, there may be a fissure, crack, or irritation on the nipple. Endemic mastitis has been the main form encountered in recent reports. In epidemic mastitis, *S. aureus* has been the main culprit. For endemic mastitis, *S. aureus* again is a common pathogen, in either pure or mixed culture, but other common organisms include group A or group B streptococci. *Haemophilus influenzae* and *Haemophilus parainfluenzae* have been reported, but in up to 50% of cases only normal skin flora are cultured from breast milk (55,56). Further insight into the relationship of breast symptoms, milk leukocytes, and quantitative breast milk cultures was provided by Thomsen and colleagues (57). In 491 samples from nursing women, women without breast symptoms had leukocytic counts below 10^6 per milliliter of milk, and milk was sterile or contained fewer than 10^3 bacterial per milliliter. When bacteria were present in milk from asymptomatic women, the organisms were similar to those normally present on the skin, and most milk specimens revealed mixed cultures. Samples from women with breast symptoms were divided into three groups. In one group (n = 85), leukocyte counts were below 10^6 per milliliter from milk, and milk cultures were similar to those from women without symptoms. Breast symptoms in this group were brief (average, 2.1 days) and resolved spontaneously. This group was said to have milk stasis. In the remaining two groups, breast milk showed more than 10^6 leukocytes per milliliter. In one of these groups (n = 22), the milk cultures were sterile or revealed fewer than 10^3 bacteria per milliliter. The average duration of symptoms was 5.3 days. This group was said to have noninfectious inflammation of the breast. In the third group (n = 39), milk cultures showed both more than 10^6 leukocytes and more than 10^3 bacteria per milliliter. Without therapy, approximately half the patients in this group showed complete recovery after an average of 5.9 days, but symptoms of sepsis and breast abscess developed in 22% and 11% of cases, respectively. In the 39 samples of milk in this group of women, organisms identified were *S. aureus* 18; coagulase-negative staphylococci 10; *Streptococcus faecalis* 2; group A streptococci 1, *E. coli* 3; *Klebsiella pneumoniae* 2; and *B. fragilis* 3.

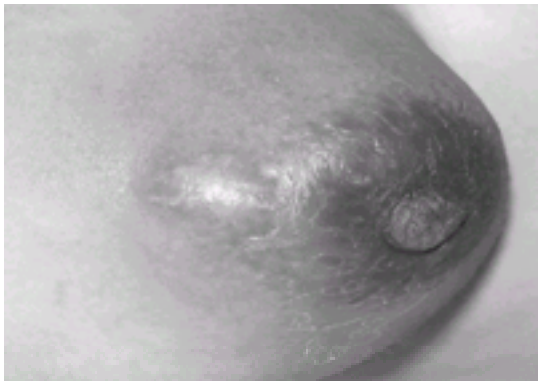


FIGURE 20.9. Postpartum breast abscess with surrounding cellulitis.

Sporadic mastitis most often begins from the second or third week to a number of months after delivery. Fever commonly above 102°F, malaise, and localized breast signs are the usual presenting problems. In untreated patients, breast abscess develops commonly. Stasis of milk after weaning often is suggested as the precipitating event for mastitis, but, only a minority of women (perhaps 20%) with mastitis have recently stopped nursing. Culture of expressed breast milk is appropriate, although only in a few cases will the report alter management.

With early antibiotic treatment, endemic mastitis resolves within 24 to 48 hours, and that abscess is unusual. In one series of 71 cases, abscess developed in only eight (11.5%); and in six of these patients, treatment was not instituted for more than 24 hours (55). Based on the organisms involved and the well-known resistance of even community-acquired staphylococci to penicillin, the choice of initial antibiotic therapy would seem to be a penicillinase-resistant penicillin (such as dicloxacillin) or a cephalosporin. However, empiric therapy with penicillin V, erythromycin, or sulfonamides has resulted in prompt responses, even when there has been *in vitro* resistance. In view of the work of Thomsen and coworkers (57), it is likely that many such cases would have resolved, even without antibiotic therapy. In most cases of mastitis, antibiotics should be given orally, as there is no need for hospitalization.

In addition to antibiotic therapy, adjunctive measures, such as ice packs, breast support, and analgesics, have been suggested. In most cases, the mother may continue to nurse from both breasts. If the infected side is too sore, she may pump this breast gently. Infants do not seem to suffer any adverse effects from suckling an infected breast, unless an abscess has developed. When an abscess develops, prompt incision and drainage should be instituted.

Urinary Tract Infection

Urinary tract infection is a common cause of postpartum fever, as the parturient is predisposed to infection by the physiologic hydroureter of pregnancy, catheterization in labor, and antecedent asymptomatic bacteriuria. A presumptive diagnosis of urinary infection can be based on traditional signs and symptoms (frequency, dysuria, back pain, fever, and costovertebral angle tenderness). Urinalysis and urine cultures are helpful in the diagnosis. Because urine specimens from puerperal women often contain contamination from the lochia, supervision at collection is important. Pyuria is still a common indicator of urinary tract infection, but it may develop without infection because of bladder inflammation from trauma at labor and delivery. Traditionally, specimens had to contain more than 10^5 CFU/mL of a single organism to be considered significant; however, evidence in nonpregnant patients suggests that more than 10^2 CFU/mL was a more specific and sensitive diagnostic criterion of infection than more than 10^5 CFU/mL in symptomatic patients (58). In most cases, *E. coli* is isolated, although other Gram-negative aerobic bacilli, enterococci, and occasionally GBS may cause urinary tract infection. Because bacteremia is possible in pyelonephritis, the initial antibiotic in febrile patients should

be one able to achieve high blood and urinary levels. A parenterally administered cephalosporin may be used initially with an aminoglycoside added if septic shock develops or when a resistant isolate is suspected. Ampicillin by itself is no longer considered adequate therapy because of widespread resistance of uropathogens. (Urinary tract infection is discussed fully in Chapter 15.)

Anesthesia Complications

Infections resulting from spinal or epidural anesthesia are extremely rare. In a series of 10,000 spinal and 32,000 epidural anesthesias, there were no infections due to the anesthetics (59), but there has been a report of a spontaneous puerperal epidural abscess (60). With general anesthesia, atelectasis and pulmonary infections may occur and present as a puerperal fever.

On rare occasions, infections beneath the gluteus or behind the psoas muscle develop in postpartum women (61). These severe infections are characterized by persistent, spiking temperature elevations and hip pain or poorly localized pelvic pain. In the reported cases, these severe infections had one common feature: the use of paracervical or transvaginal pudendal blocks. The needle penetration may be the source of contamination. In half the cases, a radiograph documented gas in the soft tissues. These patients had extensive hospitalization, and deaths have been reported. In addition to vigorous antibiotic therapy, drainage is required for treatment.

Septic Pelvic Thrombophlebitis

Pelvic vein thrombophlebitis may occur in association with pelvic surgery, operative site infection following surgery, and pelvic inflammatory disease. Pelvic thrombophlebitis is an unusual circumstance, overall presenting in approximately one in 2,000 to 6,000 deliveries (62). More recent references identify the rate as approximately one in 3,000 deliveries (Table 20.6). Among patients who have diagnosed pelvic infection, the incidence of pelvic vein thrombophlebitis previously had been reported in 1% to 2% of cases (9,10). In a more recent series, this complication occurred in less than 1% of infections after delivery (3). The pathogenesis of pelvic thrombophlebitis is based on a combination of the hypercoagulable state in pregnancy and the puerperium, including increased levels of clotting factors I, II, VII, IX, and X; changes in the vein wall as a result of surgical trauma; and inflammatory reaction due to bacteria (particularly anaerobes) and stasis of blood flow induced by late pregnancy (63). Based on a recent series, serious complications of septic pelvic thrombophlebitis, including septic pulmonary emboli, lung abscess, and empyema, are distinctly unusual after diagnosed ovarian vein thrombosis or septic pelvic thrombophlebitis in the puerperium (3,64,65).

Feature	Results
Incidence	Overall, 1:2,000 deliveries [3] After vaginal delivery, 1:7,000 to 1:15,000 [3,65] After cesarean section, 1:800 [3]
Diagnostic criteria	Persistent puerperal fever, possibly with an adnexal mass, and confirmatory radiographic findings. See text.
Suggested treatment	
Traditional	Broad-spectrum intravenous antibiotic therapy plus intravenous heparin (e.g., 5,000 U IV bolus followed by initial dose of 1,000 U/hr, and adjusted to achieve partial thromboplastin time (PTT) of 1.5 to 2 times the baseline [3,65]. Except under unusual circumstances, patients are discharged without oral anticoagulants [3].
Revised	Broad-spectrum intravenous antibiotic therapy alone (without heparinization) [3]

TABLE 20.6. SEPTIC PELVIC THROMBOPHLEBITIS

Clinical Presentation

Pelvic vein thrombophlebitis appears to occur in two distinct clinical forms. The most commonly described disorder is acute thrombosis of one or both ovarian veins. Because such large-scale thrombus formation occurs most commonly on the right side, many authors have referred to this disease process as the right ovarian vein syndrome.

Patients with acute ovarian vein thrombophlebitis usually have distinct clinical findings. Although not all individuals are febrile, most will have a mild-to-moderate temperature elevation in the first 48 to 96 hours postoperatively and experience lower abdominal pain. The initial physical examination usually is consistent with endomyometritis or pelvic cellulitis, and the attending physician quite properly initiates antibiotic therapy. Despite administration of systemic antibiotics, however, the patients do not improve. Temperature elevations may persist, often accompanied by shaking chills. Subjectively, patients experience steadily worsening abdominal pain, which is constant and localized to the side of the affected vein. The pain may radiate into the groin, upper abdomen, or flank. Gastrointestinal symptoms, such as nausea, vomiting, or distention, may be present.

On physical examination, patients usually are febrile and appear acutely ill. The pulse rate usually is elevated, often disproportionately, compared with the actual temperature. Tachypnea, stridor, and other signs of respiratory distress may be present when pulmonary embolization has occurred. Changing cardiac murmurs suggest acute endocarditis.

The most striking findings are demonstrable on abdominopelvic examination. Bowel sounds usually are normoactive, but may be diminished to absent in the presence of a paralytic ileus. Patients usually have direct tenderness on the affected side in association with both voluntary and involuntary guarding. The most definitive sign on physical examination is the detection of a rope-like tender abdominal mass. Such a mass will be palpable in one half to two thirds of patients. the mass usually originates centrally near the uterine cornua and extends laterally and cephalad toward the

upper abdomen (62).

The second presentation of pelvic vein thrombophlebitis is less distinct and has been called “enigmatic fever” (66). Initially, patients demonstrate many of the same clinical manifestations as the individuals described earlier. They have evidence of operative site infection following surgery and are given antibiotic therapy. Unlike the patients with acute ovarian vein thrombosis, however, these women usually experience definite improvement in all clinical parameters, with the singular exception of spiking temperatures. Patients do not appear to be critically ill, and positive physical findings usually are absent except for recurrent temperature elevations, often as high as 103 to 104°F, and associated tachycardia. Whereas most patients with acute ovarian vein thrombosis have palpable abdominal masses, very few of the patients with this second syndrome have demonstrable masses.

Diagnosis

The diagnosis of pelvic vein thrombophlebitis should be suspected in any patient with an antecedent soft tissue pelvic infection and an elevated temperature that persists despite appropriate broad-spectrum antibiotic therapy.

The disorder most likely to be confused with the right ovarian vein syndrome is acute appendicitis (62). Other common disorders that should be considered are broad ligament cellulitis or hematoma, torsion of the adnexa, ureterolithiasis, pyelonephritis, degenerating pedunculated leiomyoma, pelvic cellulitis, and pelvic or abdominal abscess. The disorders most likely to be confused with the second clinical syndrome are drug fever, collagen vascular disease, coexisting viral illness, and pelvic abscess (66).

The diagnosis of pelvic vein thrombophlebitis has been based largely on the patient's clinical history and physical examination. A pattern of persistent fever in association with lower abdominal pain and a palpable mass in either or both mid-quadrants is highly suggestive of a thrombotic disorder. Laboratory data are helpful in excluding other diagnoses.

Other diagnostic studies that may be of help in evaluating the patient with suspected pelvic vein thrombophlebitis include computerized axial tomography and sonography (50). Several case reports and series have demonstrated apparent thromboses by either of these techniques (67). Radiographic criteria for the diagnosis of venous thrombosis have included enlargement of the vein, low-density lumen within the vessel wall, and a sharply defined vessel wall enhanced by contrast media (50).

Treatment

Several surgical and medical approaches have been used in the treatment of pelvic vein thrombophlebitis (62,63,66). Because bacterial injury to the venous endothelium is likely to be an important mechanism in initiating the thromboembolic process in most patients, we believe that broad-spectrum antibiotics should be administered.

In previous editions, we recommended that therapeutic anticoagulation with heparin should be initiated when the diagnosis of pelvic vein thrombophlebitis is made. However, a recent randomized trial demonstrated that in women with a diagnosis of

septic pelvic thrombophlebitis, heparin given in addition to antimicrobial therapy did not have better outcomes than women for whom antimicrobial therapy alone was continued (3). In a small but adequate trial, 14 women were randomly assigned to either continued antibiotic therapy alone (without the addition of heparin) (n = 8) or heparin therapy in a full anticoagulation regimen in addition to antimicrobial agents (n = 6). According to an intent-to-treat analysis, there was no significant difference between the groups with regard to number of hours febrile (104 ± 39 hours for those given antimicrobial agents alone vs. 134 ± 65 hours for those also given heparin; p = 0.83) or in duration of hospitalization (10.6 ± 1.9 days for those given antimicrobial agents alone vs. 11.3 ± 1.2 days for those also treated with heparin; $p > 0.5$). These women were followed up for at least 3 months postpartum, and none showed evidence of reinfection, embolic episodes, or phlebitic syndrome (3). The authors concluded that these results do not support the common practice of heparin treatment for women with presumed septic pelvic thrombophlebitis, and we recently adopted their recommendations (3) (Table 20.6). Surgical intervention should be reserved for patients who remain clinically ill despite effective medical therapy (66) or for women with an acute abdomen. Multiple surgical procedures have been proposed as the optimal technique, including bilateral ovarian vein ligation and inferior vena cava ligation; unilateral ovarian vein ligation with and without vena cava ligation; and excision of the infected vein ligation with and without ligation of the contralateral vein and vena cava. The most reasonable approach would seem to be ligation of the infected vein(s) and concurrent ligation of the vena cava only when the ovarian vein thrombolus extends into this large vessel (62).

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21

WOUND AND EPISIOTOMY INFECTION

Infections of abdominal incisions and episiotomies occur regularly in obstetric-gynecologic practice. This chapter emphasizes the major topics of physiology of wound healing; pathogenesis of care of wound infections, including early recognition of unusual but life-threatening infections such as necrotizing fasciitis; and early healing by secondary closure.

Normal Wound Healing

As reviewed by Singer and Clark (1), wound healing is a dynamic process characterized by three phases: inflammation, tissue formation, and tissue remodeling. These phases may overlap in time. In the inflammation phase, tissue injury leads to disruption of vessels and collection of blood constituents in the wound. The blood clot establishes hemostasis and leads to an extracellular matrix for cell migration. The coagulation and activated complement pathways and injured or activated parenchymal cells generate a number of vasoactive mediators and chemotactic factors. It is these substances that recruit inflammatory leukocytes into the wound. Infiltrating polymorphonuclear leukocytes cleanse the wound of foreign particles and bacteria. Further, in response to specific chemoattractants, mononuclear white blood cells infiltrate the wound and turn into activated macrophages, which are the source of growth factors such as platelet-derived growth factor and vascular endothelial growth factor. These substances initiate formation of granulation tissue (Table 21.1). Monocytes adhere to the extracellular matrix and change into inflammatory or reparative macrophages. Several cytokines then are stimulated, including colony-stimulating factor 1, which is necessary for survival of monocytes and macrophages; tumor necrosis factor alpha; and platelet-derived growth factor, which is a chemoattractant and a mitogen for fibroblasts. Macrophages play a pivotal role in the process occurring between inflammation and repair. Within hours after injury, reepithelialization of the wound begins. Epidermal cells rapidly begin to remove clotted blood and damaged stroma. Degradation of the

extracellular matrix, required for the migration of epidermal cells into the wound, depends on the production of collagenase. Within 1 to 2 days after injury, epidermal cells at the wound margin begin to proliferate. Next, granulation tissue begins to appear and invade the wound. Granulation tissue, which is actually new stroma, develops approximately 4 days after injury. The commonly recognized granular appearance is due to numerous capillaries in the new stroma. At the same time, macrophages, fibroblasts, and blood vessels move into the wound space. The role of the macrophages is to provide a continuing source of growth factors necessary for fibroplasia and angiogenesis. The role of the fibroblasts is to produce an extracellular matrix upon which support cell growth occurs. The blood vessels bring nutrients and oxygen to sustain cellular metabolism. Formation of new blood vessels is necessary to sustain the newly formed granulation tissue. This process of angiogenesis is complex and relies on the extracellular matrix plus migration and mitogenic stimulation of endothelial cells. During the second week of healing, fibroblasts appear as large bundles of actin-containing microfilaments, and this marks the commencement of connective tissue compaction and contraction of the wound. Wounds gain only about one fourth of their final strength in the first 3 weeks when collagen has accumulated rapidly and has been remodeled by a wound contraction. Wounds then gradually gain further tensile strength as a result of slower rates of accumulation of collagen and further collagen remodeling. Wounds do not attain the same tensile strength as uninjured tissue. It is estimated that maximally a scar is only 70% as strong as normal skin.

TABLE 21.1. CYTOKINES THAT AFFECT WOUND HEALING

Wound Infections

Abdominal wound infection following cesarean section or gynecologic surgery is a common complication that accounts for significant extension of hospital stays and adds considerable cost to hospital bills. Classic reports of abdominal surgery have revealed wound infection in 4.8% to 7.5% of cases (2,3). The wound infection rate was 6.1% for abdominal hysterectomy and 3.1% for oophorectomy (2). After cesarean section, wound infection has been reported in an average of 10% (range 0%–15%) of patients in control groups in prophylaxis studies (4). In a prospective incidence study in England and Wales, Moir-Bussy and colleagues (5) found that 17.4% (413/2,370) of patients had signs of inflammation (i.e., localized erythema and

induration develop). Defining wound infection on the basis of two of the following three criteria: erythematous wound cellulitis, purulent discharge, or positive wound culture, Emmons et al. (6) at the University of Washington noted a rate of 5.4% (60/1,104 cesarean deliveries). In Australia, Webster (7) reported a rate of 9.4% (146/1,546), with a higher rate in clinic patients (15.8%) than in private patients (6.0%) and a higher rate in emergency cases (12.3%) than in elective cases (7.9%). Roberts and coworkers (8) reported a rate of 6.9% (65/939) for wound morbidity, defined as erythema, induration, or pain and demonstrable fluid noted on ultrasound. This rate is noteworthy, as it is derived from a large number of patients at a public hospital in the United States at a time when all patients had received intravenous antibiotic prophylaxis (1 g of cefotetan after cord clamping) (8).

According to the definition of wound infection adopted by the National Research Council in 1964, a wound is defined as “infected” if pus discharges and as “possibly infected” if the wound develops the signs of inflammation or serous discharge (2). In 1964, the Ad Hoc Committee of the Committee on Trauma of the National Research Council formulated a standard classification of surgical wounds into four categories (2) (Box 1):

Box 1

Classification of Surgical Wounds

- *Clean:* The gastrointestinal, respiratory, or genitourinary tract is not entered. No inflammation is encountered, and no break in aseptic technique occurs.
- *Clean-contaminated:* The gastrointestinal or respiratory tract is entered without significant spillage. Included in this category are procedures involving entry into the vagina or the uninfected biliary tract. Cesarean section in the presence of ruptured membranes falls into this category.
- *Contaminated:* Acute inflammation (without pus formation) is encountered. There is a major break in aseptic technique, or gross spillage from the gastrointestinal tract occurs. Incisions into infected biliary or urinary tracts are included in this category. A cesarean section performed in the presence of chorioamnionitis belongs in the contaminated group.
- *Dirty:* Presence of pus, a perforated viscus, and traumatic wounds are included in this category. The definition implies the presence of organisms in ordinarily sterile tissue prior to the operation.

Clean wound: The gastrointestinal, respiratory, or genitourinary tract is not entered. No inflammation is encountered, and no break in aseptic technique occurs. In a large prospective study, Cruse and Foord (9) noted that only 624 (1.7%) of 36,383 clean wounds became infected. *Clean-contaminated:* The gastrointestinal or respiratory tract is entered without significant spillage. Included in this category are procedures involving entry into the vagina or the uninfected biliary tract. Cesarean section in the presence of ruptured membranes falls into this category. Cruse and Foord (9) observed that wound infection was diagnosed in 646 (8.8%) of 7,335 clean-contaminated wounds. An expected rate of 10% is the generally quoted

estimate of infection in these cases. *Contaminated:* Acute inflammation (without pus formation) is encountered. There is a major break in aseptic technique, or gross spillage from the gastrointestinal tract occurs. Incisions into infected biliary or urinary tracts are included in this category. A cesarean section performed in the presence of chorioamnionitis belongs in the contaminated group. The expected infection rate in contaminated cases is about 20%. Cruse and Foord (9) reported that 458 (17.5%) of 2,613 contaminated wounds became infected. *Dirty:* Presence of pus, a perforated viscus, and traumatic wounds are included in this category. The definition implies the presence of organisms in ordinarily sterile tissue prior to the operation. A 30% infection rate is considered a reasonable estimate. Cruse and Foord (9) documented that infection occurred in 660 (41.6%) of 1,586 dirty wounds.

Cost

The cost of wound abscess results primarily from extension of hospital stay, but other costs, including antibiotics, supplies, and additional treatments, such as operations, may be incurred. Haley and colleagues (10) estimated the direct costs of surgical wounds of all types to be $884 in 1980.

Pathogenesis

Two major factors determine whether a wound will become infected: the amount of bacterial contamination and the resistance of the patient. Bacterial contamination is either endogenous, from the patient's own microbial flora, or exogenous, from the environment. The influence of endogenous contamination is readily documented by the progressive increase from a clean infection rate through a 30% rate in dirty operative cases. In general, the source of endogenous bacteria in obstetric or gynecologic abdominal wound infections is either the abdominal skin or the flora of the vagina and cervix.

The condition of the wound is important in determining local resistance and to a large extent is a reflection of surgical technique. Gentle tissue handling, complete hemostasis, debridement of devitalized tissue, adequate blood supply, obliteration of dead space, and closing of the wound without tension are principles of good surgical technique. Hematomas or foreign bodies in the wound predispose to the development of infection. Hemoglobin interferes with leukocyte migration and phagocytosis. An inadequate blood supply leads to lower oxygen tension and acidosis in the wound, with the resultant inability of macrophages to kill bacteria.

In general surgery, risk factors for wound abscess have been reported in classic studies (2,3). Factors identified are bacterial contamination of the wound, age, obesity, operating time, use of drains, duration of preoperative hospitalization, diabetes, and malnutrition. Use of steroids was associated with an increase in wound infections in the study by Howard et al. (2), but not in the study by Cruse and Foord (3). Howard et al. (2) found an increase in wound infections when there was an infection that was remote from the operative incision. Cruse and Foord (3) noted increases in infection rates with puncture of the surgeon's gloves and shaving or clipping of hair at the operative site (compared with use of a depilatory cream or no hair removal).

Risk factors for wound abscess after cesarean delivery may be different than the risk

factors for abscess after other surgical procedures. Patients undergoing cesarean delivery have a limited age range, usually experience only a brief preoperative hospital stay, and rarely have debilitating diseases; furthermore, the operation itself is relatively short. On the other hand, many cesarean sections are performed as emergency procedures, often in a field contaminated with large numbers of bacteria (11,12). It is likely that this fluid leads to contamination of the wound and, in some patients, wound abscess.

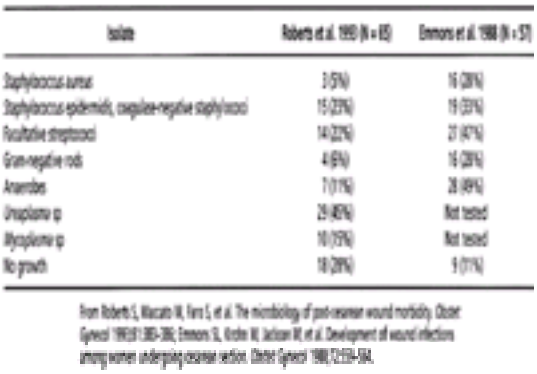
Using a retrospective case-control design, Gibbs et al. (13) found that selected features of labor were strongly associated with wound abscess after cesarean section. These features were duration of labor, interval from rupture of membranes to delivery, number of vaginal examinations, and duration of internal fetal monitoring. These features also were associated with intrauterine infection on the authors' service (13). Other risk factors were operating time and estimated blood loss, but age, parity, weight, preoperative stay, preoperative hematocrit, surgeon's years of training, time of day, type of anesthesia, and presence of other maternal disease (hypertension, diabetes, etc.) were not significantly associated with wound abscess. Thirty-one percent of patients with abscess had transverse skin incision versus 17% of controls ($p = 0.08$) (13).

In England and Wales, Moir-Bussy and colleagues (5) reported a prospective study of wound infections after cesarean section. The authors defined a “wound infection” as signs of inflammation or purulence plus a ositive culture. Of 2,370 patients, 6% had wound infection, whereas 17.4% had signs of inflammation (but no pathogenic organisms isolated). There was no relationship between hospital cesarean section rate (which varied from 4.4% to 19.6%) and the wound inflammation rate (which varied from 1.4% to 38.5%). Most inflamed or infected wounds became apparent on postoperative days 4 to 7, but 23% were evident on or before day 3 and 10% on or after day 8. Patients with wound infections spent an extra 2.4 days in the hospital (10.5 vs. 8.1 days). Analysis of risk factors was performed by univariate techniques only. No significant associations were found between wound infection and category of operation (emergency vs. trial of labor vs. elective), age, number of previous cesarean sections, use of internal fetal monitoring, or presence of ruptured membranes. However, significant associations were noted with increased mean time in labor (7.4 vs. 5.3 hours; $p < 0.01$), increased number of vaginal examinations (2.5 vs. 2.1; $p < 0.05$), use of midline or paramedian incision versus transverse incision ($p < 0.05$), and obesity ($p < 0.0001$). Further, use of drains was accompanied by increased wound infection (8.8% vs. 5.3%; $p < 0.05$).

Microbiology

In 1988, Emmons et al. (6) reported a retrospective study of the microbiology of 60 cases of wound infection after cesarean delivery. The authors noted that wound infections caused by cervical/vaginal flora were associated with prolonged labor, longer duration of fetal monitoring, larger number of vaginal examinations, and with organisms isolated from the endometrium at cesarean section. In comparison, infections associated with *Staphylococcus aureus,* which accounted for 25% of wound infections, had neither prolonged labor nor *S. aureus* isolated at cesarean section. They reasoned that the former wound infections resulted from ascending infection from genital organisms, whereas the infections with *S. aureus* presumably arose from exogenous sources. Roberts et al. (8) obtained wound aspirates by inserting a sterile needle through the healing incision if there were signs of infection.

Wound aspirates showed a positive culture in 72% (47/65) of cases. The predominant isolates were organisms commonly found in the lower genital tract, with the genital mycoplasmas being most common. Organisms commonly found in the skin (but also in the genital tract) were isolated less frequently: coagulase-negative staphylococci in 32% of positive cultures and *S. aureus* in only 6% (Table 21.2). The large differences in results may be due to the populations studied, collection techniques, or laboratory methods.



Isolate	Roberts et al. 1993 (N = 65)	Emmons et al. 1988 (N = 57)
Staphylococcus aureus	3 (5%)	16 (28%)
Staphylococcus epidermidis, coagulase-negative staphylococci	15 (23%)	19 (33%)
Facultative streptococci	14 (22%)	27 (47%)
Gram-negative rods	4 (6%)	16 (28%)
Anaerobes	7 (11%)	28 (49%)
Ureaplasma sp	25 (40%)	Not tested
Mycoplasma sp	10 (15%)	Not tested
No growth	18 (28%)	9 (11%)

From Roberts S, Maccato M, Faro S, et al. The microbiology of post-cesarean wound morbidity. Obstet Gynecol 1993;81:380–386; Emmons SL, Gordon HE, Jackson ME, et al. Development of wound infections among women undergoing cesarean section. Obstet Gynecol 1988;72:559–564.

TABLE 21.2. MICROBIOLOGY OF WOUND INFECTION AFTER CESAREAN DELIVERY

Clinical Presentation and Treatment

Early-onset wound infection occurs within the first 48 hours postoperatively, often in the initial 12 to 24 hours. Patients present with an elevated temperature and an alteration in appearance of the abdominal wound. This may be a spreading cellulitis or discoloration of the skin in association with an advancing margin of active infection. Early-onset wound infection usually is caused by a single bacterial pathogen, most commonly group A streptococcus or *Clostridium perfringens* (Fig. 21.1). Gram stain of material aspirated from the active margin of infection may be diagnostic. Gram-positive rods are strongly suggestive of clostridia; gram-positive cocci indicate the probable presence of group A streptococci. Infection due to group A streptococci should be suspected if the patient develops a diffuse cellulitis, systemic illness, or both. Group B streptococci may present a similar picture. In clostridial infection, cellulitis of the skin and subcutaneous tissue is associated with a watery discharge, followed by the characteristic bronze appearance of the skin and crepitation in the vicinity of the wound.

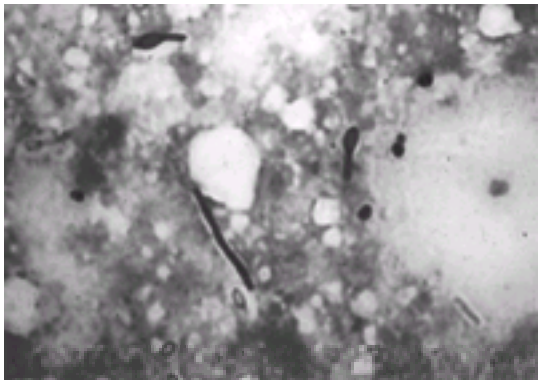


FIGURE 21.1. Gram-positive rods, some with spores, characteristic of *Clostridum perfringens*.

The treatment of early-onset wound infection consists of antibiotics and excision of necrotic tissue. Penicillin is the antibiotic of choice for both clostridia and group A streptococcus; alternatives include ampicillin, cephalosporins, erythromycin, or chloramphenicol. Extensive debridement and excision of necrotic tissue may be required. It is crucial to remove all nonviable tissue. Failure to treat these early-onset wound infections aggressively exposes patients to the risks of necrotizing fasciitis, bacteremia, and disseminated intravascular coagulation.

Late-Onset Wound Infection

Late-onset wound infections occur about 4 to 8 days postoperatively. They present with fever and a swollen, erythematous, draining wound. The basic treatment modality for late-onset wound infection is incision and drainage. Antibiotics generally are not required, unless there is extensive coexistent cellulitis or an additional source of infection. Once the wound has been opened and drained and nonviable tissue excised, the patient should rapidly become afebrile, usually within 12 to 24 hours. If a response does not occur within this time, broad-spectrum antibiotic therapy aimed at mixed aerobic-anaerobic bacteria should be instituted, and the possibility of a more extensive infectious process such as *necrotizing fasciitis* must be entertained.

Management of the Opened Abdominal Wound

Historically, the approach to the opened wound has been closure by secondary intent, i.e., wound debridement, packing, and allowing it to close by granulation. Although this approach led to successful closure, it often took a long time and required frequent and numerous visits. Several studies have systematically compared closure by secondary intent with surgical closure after the wound was clean (i.e., secondary closure). In 1990, Walters and coworkers (14) used an *en bloc* closure technique after the wound was granulating well (with a minimum of 4 days) and compared it with closure by secondary intent. Reclosure was successful in 30 (86%) of 35 cases (Table 21.3). Even when wound closure was not successful, the time to complete wound healing still was no longer than that with secondary intent

(14).

	Reclosure (N = 35)	p	Second Intent (N = 6)
Successful closure	30 (86%)		–
Time to complete healing (mean days)	23 ± 4	0.002	72 ± 7
Successful (n = 30)	16 ± 0.5		
Failed (n = 5)*	68 ± 15		

*Weight >200 lbs more likely to fail; p = 0.038.
From Walters MD, Dombrocki RA, Davidson SA, et al. Reclosure of disrupted abdominal incisions. Obstet Gynecol 1998;76:597.

TABLE 21.3. RECLOSURE OF DISRUPTED ABDOMINAL INCISIONS

The procedure has been carried out under general, regional, or local anesthesia. We used a single-filament nonabsorbable suture (such as no. 2 nylon) with swedged needles. The suture placement was a “far-far-near-near” technique. The first “far” stitches were placed about 2 inches from the wound edge, through skin and subcutaneous tissue. A small bite of fascia was taken in the midline to anchor the stitch, and the suture was brought out again 2 inches from the wound margin. A rubber shod was placed on the suture, and the “near” bites were taken about ¼ inch from the margin. A second rubber shod was placed, and the suture was tied. Usually, three to five sutures were placed. No additional skin sutures were used. Prophylaxis with a first-generation cephalosporin was used. The sutures were removed on approximately the tenth day after closure (Fig. 21.2). The results of this comparison are shown in Table 21.3. Figure 21.3 shows this closure technique.

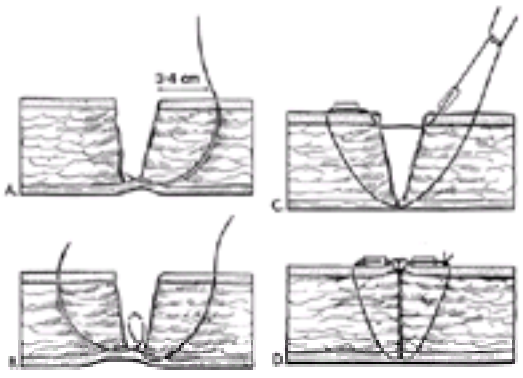


FIGURE 21.2. Technique of *en bloc* wound reclosure. **(A)** The needle is passed from a point on the skin 3 to 4 cm from the wound edge through the superior part of the fascia at the wound base. **(B)** The needle is withdrawn from the wound base, reintroduced into the fascia at the point from which it emerged with the first pass, and brought out through the skin at a point 3 to 4 cm from the opposite wound edge. **(C)** Rubber suture guards are loaded onto the suture, the suture is brought across the

incision incorporating the dermis and epidermis of the wound margins, and a second suture guard is loaded. **(D)** The suture is tied, closing the wound. (From Walters MD, Dombroski RA, Davidson SA, et al. Reclosure of disrupted abdominal incisions. *Obstet Gynecol* 1990;76:597–602, with permission.)

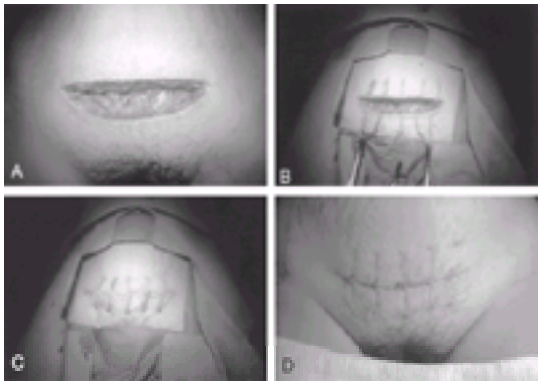


FIGURE 21.3. Walters' technique for closure. **(A)** Wound at the start of the procedure. **(B)** Sutures and rubber shods in place. **(C)** Sutures are tied. Close of the procedure. **(D)** Wound on postoperative (postclosure) day 10.

Dodson and colleagues (15) also reported a randomized comparison, but with a modified closure technique. After the wound showed a “healthy bed of granulation tissue” (defined as red, exhibiting neovascularization, and free of exudate and necrosis), the closure was carried out in the treatment room on the nursing unit (not in the operating room), after preparation with povidone-iodine, under local anesthesia. Lidocaine (Xylocaine) HCl 1% (up to 30 mL) was injected subcutaneously in a circumferential fashion from the wound edges, extending about 4 cm. A 25-gauge needle was used. No further anesthetic was injected into the deeper tissues. No prophylactic antibiotics were used. The incision was closed with simple interrupted sutures of no. 1 polypropylene (Prolene), incorporating the entire wound thickness in figure-of-eight stitches, but not including the fascia. Sutures were placed 2 cm apart and 3 to 4 cm from the wound edge (Fig. 21.4). Skin edges were approximated with Steri-Strips. Patients were discharged the day after closure and followed weekly. Sutures were removed when the wound was completely healed. Fifteen patients were assigned to wound closure and 18 to secondary intent. There were no differences between the groups with regard to demographic characteristics. Both transverse and vertical incisions were included. Patients randomized to secondary closure required less time to complete wound healing (17.6 ± 7.2 days vs. 61.2 ± 35.8 days; $p < 0.001$) and required fewer postoperative visits (2.0 ± 0.7 vs. 8.4 ± 6.2; $p < 0.001$) compared with patients in the secondary intent closure group.

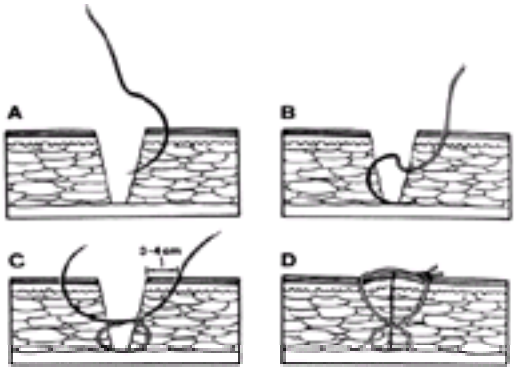


FIGURE 21.4. Technique of *en bloc* secondary closure. **(A)** The needle is passed 3 to 4 cm from the edge of the incision to the base. **(B,C)** Alternative technique if the incision is too deep for a single needle pass. **(D)** The suture is tied, obliterating dead space and approximating the edges. (From Dadson MK, Magann EF, Meeks GR. A randomized comparison of secondary closure and secondary intention in patients with superficial wound dehiscence. *Obstet Gynecol* 1992;80:321–324, with permission.)

In 1994, Dodson et al. (16) compared their *en bloc* closure with superficial wound closure in patients with extrafascial wound disruption. The superficial closure used 2-0 polypropylene suture attached to a straight cutting needle in a vertical mattress fashion, incorporating only the skin and superficial subcutaneous tissue (Fig. 21.5). The depth of placement was no more than 10 mm into the subcutaneous tissue, and the far portion of the stitch was placed 2 cm from the wound edge, with the near portion placed at 5 mm. Stitches were placed 2 cm apart. Again, Steri-Strips were placed between sutures as needed. As in the earlier study (15), all wounds were closed on the nursing unit, under local anesthesia, without use of antibiotic prophylaxis. Premedication was achieved with 50 mg of meperidine given intramuscularly. Twenty-three patients were enrolled (seven to *en bloc* and 16 to superficial closure) over 8 months. There were no significant differences between the groups with regard to patient demographics. Patients in the superficial closure group had shorter procedures (18.9 ± 3.4 min vs. 27.1 ± 5.5 min; $p < 0.001$), less pain (16.6 ± 11.4 vs. 43.4 ± 23.2 on self-scoring pain technique [scale 0–100]; $p < 0.001$), and similar times to complete healing (19.8 ± 5.3 days vs. 22.7 ± 7.7 days; p = NS).

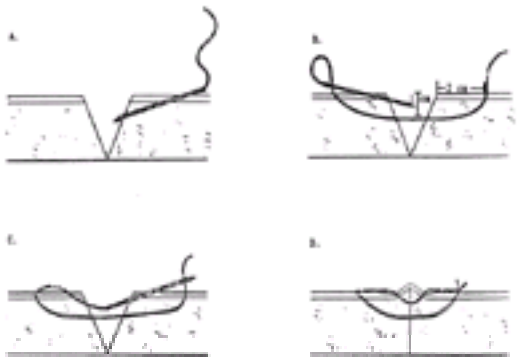


FIGURE 21.5. Superficial skin closure technique using vertical mattress sutures. (From Dodson, MK, Magann EF, Sullivan DL, et al. Extrafascial wound dehiscence: deep en bloc closure versus superficial skin closure. *Obstet Gynecol* 1994;83:142–145, with permission.)

These trials, as well as others in general surgery, have clearly demonstrated the benefits of secondary closure. Nearly all patients will tolerate closure under local anesthetic as well as the patients of Dodson et al. (15,16). Accordingly, secondary closure should be offered to patients with wound separations.

Life-Threatening Wound Complications

Prompt recognition of the clinical differences between simple wound infection and the life-threatening varieties is essential to a good outcome. Because life-threatening wound infections are rare, even a busy practitioner will encounter them infrequently, or perhaps not at all. Characteristics of these infections are summarized in Table 21.4.

Condition	Signs/Symptoms	Organism	Treatment
Meleney gangrene (nonclostridial bacterial synergistic gangrene)	Slowly progressing pain, ulcer, ecchymosis erythema	Mixed	Broad-spectrum antibiotics, excision of skin, subcutaneous tissue
Necrotizing fasciitis	Pain, edema, watery discharge—early; bullae—late	Mixed	Broad-spectrum antibiotics, excision of affected fascia with overlying skin, subcutaneous tissue
Clostridial myonecrosis (gas gangrene)	Pain, jaundice, crepitus, gas—late sign	Clostridium perfringens	Penicillin plus broad-spectrum coverage, excision of involved muscle (e.g., hysterectomy) or overlying tissues

TABLE 21.4. DIAGNOSIS AND TREATMENT OF LIFE-THREATENING WOUND INFECTION

Necrotizing fasciitis is the most commonly encountered serious wound infection. Early in the course, there are minimal cutaneous findings, which may include edema, cellulitis, and local anesthesia. Crepitation occurs occasionally. Yet the patient often is critically ill with disorientation, shock, disproportionate tachycardia or hypothermia, and multiorgan dysfunction. Stephenson et al. (17) reviewed the case histories of 29 nonpregnant women with necrotizing fasciitis of the vulva that was unrelated to postoperative or postpartum infections. Delay in recognition and in prompt and appropriate surgical intervention was accompanied by increased morbidity and mortality. Many of these “spontaneous” vulvar infections initially were thought to be labial cellulitis. Patient age ranged from 25 to 77 years. Morbid obesity (>50% above

ideal body weight) was present in 20 cases, hypertension or peripheral vascular disease in 15, chronic renal insufficiency in eight, and diabetes in 20. There were 14 deaths, 12 of which occurred when the interval between presentation and definitive surgical therapy was less than 48 hours.

The technique for dissection may be either blunt until resistance is met or sharp with excision of the full thickness until bleeding is encountered. We have found that frozen section is helpful when clinical delineation is unclear. Figure 21.6 and Figure 21.7 show the extent of surgery necessary in one of our cases of necrotizing fasciitis. Figure 21.8 shows the extent of vulvar debridement of spontaneous fasciitis in a poorly controlled diabetic patient.

FIGURE 21.6. Preoperative photograph of patient with vulvar and perineal necrotizing fasciitis. Note asymmetric edema of labia majora and necrosis of left labia minora. Further debridement of necrotic tissue was necessary.

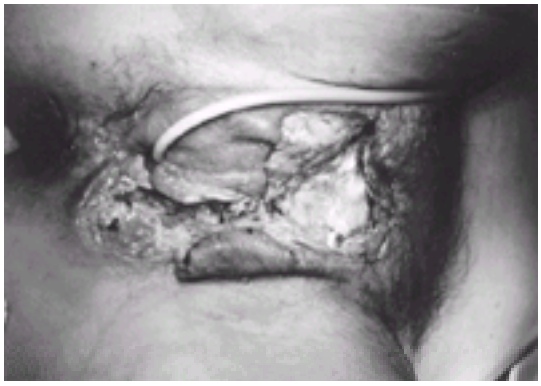


FIGURE 21.7. Second procedure of the case shown in Fig. 21.6. Further debridement of devitalized tissue was necessary.

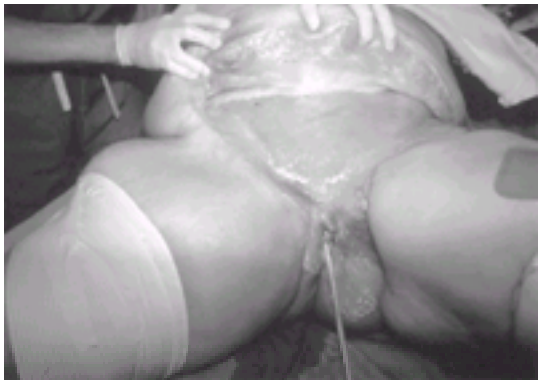


FIGURE 21.8. Extent of surgical excision in a diabetic with necrotizing fasciitis of the left vulva. Photograph taken on approximately hospital day 28, when closure was performed.

Necrotizing fasciitis is a polymicrobic infection; the bacterial isolates include anaerobes such as peptostreptococci, peptococci, clostridia, and *Bacteroides fragilis,* as well as facultative anaerobes such as group A streptococci, *Escherichia coli, Klebsiella* sp, *Proteus* sp, and *S. aureus.*

The suspected diagnosis traditionally is confirmed only at surgery, where there is "extensive undermining of the surrounding tissues, with the fascial plane lacking resistance to a blunt instrument" (18). Stamenkovic and Lew (18) advocated use of frozen-section biopsy for early recognition (and early intervention) of necrotizing fasciitis. The biopsy was taken to include infected subcutaneous tissue, fascia, and muscle beneath the involved dermis. The specimen was at least 10 × 7 × 7 mm. Biopsy was done under local anesthesia, except where local anesthesia was already present due to the disease process itself. On frozen section, the histologic criteria for diagnosis were (a) necrosis of superficial fascia; (b) polymorphonuclear infiltration of the deep dermis and fascia; (c) fibrinous thrombi of arteries and veins passing through the fascia; (d) angiitis with fibrinoid necrosis of the arterial and venous walls; (e) presence of microorganisms within the destroyed fascia and dermis in a tissue specimen with Gram stain; and (f) absence of muscle involvement (Fig. 21.9 and Fig. 21.10). Over a 13-year period, 19 cases of necrotizing fasciitis were seen. In an accompanying editorial, Pruitt (19) pointed out that the frozen sections must be interpreted cautiously, as they may be falsely negative. All negative biopsy readings must be interpreted in view of the clinical course, and permanent sections may revise the diagnosis. A second frozen-section biopsy at another site is appropriate if the first is inconsistent with the clinical presentation. This study points out the benefit of surgical biopsy in suspected fasciitis when local signs are minimal (18). Treatment must be aggressive and must include extensive drainage and debridement and administration of appropriate antibiotics, as indicated by Gram's stain and cultures, in high dosages as adjunctive therapy. In view of the mixed aerobic-anaerobic nature of these infections, an appropriate antimicrobial regimen would be a broad-spectrum combination such as clindamycin-aminoglycoside penicillin. Multiple surgical procedures usually are necessary.

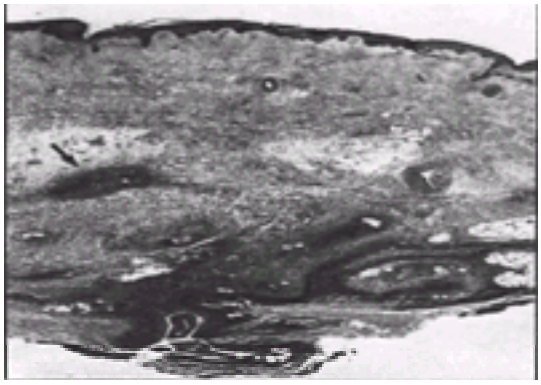


FIGURE 21.9. Histologic appearance of early necrotizing fasciitis 36 hours after the onset of disease. Necrosis and dense polymorphonuclear infiltration are confined to the deep dermis and fascial plane. Obliterating vascular thrombosis is present (*arrow*). The superficial dermis and epidermis are intact at this stage (hematoxylin and eosin, original magnification ×16). A fixed tissue section is shown because of the higher quality of the image; correlation with the frozen-tissue section was excellent, allowing accurate diagnosis in all cases in which frozen-section biopsy was performed. (From Stamenkovic I, Lew PD. Early recognition of potentially necrotizing fasciitis. The use of frozen-section biopsy. *N Engl J Med* 1984;310:1689–1693, with permission.)

FIGURE 21.10. Histologic appearance of later-stage necrotizing fasciitis in surgically resected material obtained 7 days after the onset of disease. Necrosis extends to all the soft tissue layers and involves the superficial dermis and epidermis (*arrow*). Muscle (not shown) was spared (hematoxylin and eosin, original magnification ×16). (From Stamenkovic I, Lew PD. Early recognition of potentially necrotizing fasciitis. The use of frozen-section biopsy. *N Engl J Med* 1984;310:1689–1693, with permission.)

Another form of severe wound infection is progressive synergistic bacterial gangrene. Classically described by Meleney and coworkers, this process appears to have a central ulcer, surrounded by a characteristic deep red or purple zone (Fig.

21.11). In turn, this is surrounded by an outer zone of erythema (20,21). At times, the ulcerated area is dark gray or even black. The process is slowly progressive, and often there is severe pain. A mixture of organisms may be responsible, and appropriate therapy consists of broad-spectrum antibiotics and sharp debridement. Serial debriding procedures in the operating room often are necessary to contain this process.

FIGURE 21.11. Progressive synergistic bacterial gangrene in a patient with stage IV carcinoma of the cervix. A central ulcerated area is seen in the left crural region and is surrounded by an irregular darker zone.

More fulminant is clostridial gas gangrene (clostridial anaerobic myonecrosis) (20). *Clostridium perfringens* is responsible in 60% to 80% of cases, with other clostridial species responsible for the rest. The clinical signs are sudden onset of severe pain in the wound, mild local edema, and thin watery exudate issuing from the wound. Systemic signs usually are present and vary from fever and tachycardia to septic shock. In advanced states, the wound has a bronzed appearance, with blue or black bullae, cutaneous gangrene, and crepitus. A radiograph may show gas, but this is a late sign. The mainstay of treatment is adequate surgical debridement. Because of systemic findings, antibiotic therapy is necessary; penicillin G (20 million units intravenously in divided doses) is preferred. Hyperbaric chambers and polyvalent antitoxin are of unproved value.

Prevention

Standard approaches to decrease the risk of postoperative abdominal wound infection include limiting the duration of preoperative hospitalization; when possible, correcting malnutrition or anemia; stabilizing diabetes; decreasing steroids or immunosuppressive agents, if possible; eradicating all infection such as urinary tract infection; proper preparation of the skin; proper surgeons' scrubbing technique; limiting operating room traffic; using appropriate operating room ventilation and airflow; and using proper surgical technique. Prophylactic antibiotics are of value in some operations, as discussed in Chapter 24.

Closed drainage of the subcutaneous tissue is commonly used to prevent wound infection and wound breakdown. Few controlled studies have assessed this

technique. Those advocating such drainage point to the elimination of dead space and reduction of fluid accumulation, which is recognized as an excellent culture medium for bacteria. On the other hand, opponents of routine wound drainage suggest that these drains may facilitate bacterial migration into the wound. In 1996, Gallup and colleagues (22) carried out a prospective randomized trial of subcutaneous drains (using either a Jackson-Pratt or a Blake drain) in women who weighed more than 30% above ideal body weight and who had undergone gynecologic surgery. Drains were left in place for 72 hours or until drainage was less than 50 mL/day. Prophylactic antibiotics were used in a nonrandomized fashion and given at the discretion of the attending physician. Overall, wound breakdown occurred in 6.4% (7/109 cases) when drains were used compared with 11.4% (10/88 cases) when drains were not used. This nearly twofold decrease in wound breakdown rate accompanying use of drains was not statistically significant ($p = 0.2$). When total complications were compared, 20% (22/109 cases) in the group with drains had complications compared with 31% (27/88 cases) without drains. This difference still did not achieve statistical significance ($p = 0.09$) (22).

Where there is a high likelihood of wound infection, such as pelvic abscess, a delayed primary wound closure may be indicated (23). This approach will significantly reduce the risk of wound infection. On the fourth postoperative day, if the wound appears clean, it is closed. There is no increase in hospital stay required by the approach, and the wound heals very much like a primary closure.

Episiotomy Infections

Episiotomy with repair is performed commonly in vaginal deliveries. Infection is an infrequent complication of this operation, but occasional severe consequences can occur (24,25 and 26). Because the anatomic structures of the perineum are the same as those of the abdominal wall, episiotomy infections are similar in type to wound infections.

Simple Episiotomy Infection

Simple episiotomy infection is a localized infection involving only the skin and subcutaneous tissue (including Scarpa fascia of the perineum) adjacent to the episiotomy. Signs are local edema and erythema with exudate; more extensive findings should raise suspicion of a deeper infection. Treatment consists of opening, exploring, and debriding the perineal wound. Drainage alone usually is adequate, but appropriate antibiotics are indicated if there is marked, superficial cellulitis or isolation of group A streptococci. The episiotomy incision should not be resutured at this time. Most will heal by granulation. Incisions involving the sphincter muscle or rectal mucosa can be repaired when the field is free of infection. In recent reports, it has been demonstrated that breakdown of fourth-degree episiotomies, whether the result of infection or dehiscence, can be safely and effectively repaired early in the course (27,28 and 29). When repair was accomplished a mean of 6 days after breakdown (range 3–13), the success rate was 94% (32/34 cases) (27). Arona and colleagues (30) also demonstrated that early secondary repair of third-degree and fourth-degree perinatal lacerations can be carried out satisfactorily after outpatient wound preparation. In a series of 23 patients, daily outpatient debridement was carried out, removing all necrotic tissue and remaining suture material. The procedure was carried out with local anesthetic, if necessary. Daily wound care included copious irrigation using half-strength Dakin solution. Patients were

requested to avoid intercourse and to take a sitz bath in warm water three times per day and after bowel movements. The mean number of days of wound preparation was 7 (range 4–10). The endpoint in wound preparation was the presence of pink granulation tissue throughout. An oral antibiotic was used in only one patient.

The techniques have been similar in recent series. Initial debridement consists of removal of all infected and necrotic tissue and suture fragments and copious irrigation with diluted Betadine, either in the operating room under regional anesthesia or on the nursing unit with intravenous analgesia. Intravenous antibiotics were continued in nearly all cases. Subsequent daily wound care consisted of twice-daily scrubbing with a Betadine-impregnated brush. Topical 1% Xylocaine jelly was used in all patients and additional intravenous meperidine in some patients for these scrubbings. Sitz baths were used several times daily. Repair was carried out when the patient had been afebrile for 24 to 48 hours, and the wound was clean and covered with granulating tissue. The evening before repair, patients with fourth-degree extensions had mechanical bowel preparation with an oral electrolyte solution (Golytely; Braintree Laboratories, Braintree, MA, USA) given as 1 gallon to be consumed until the patient had clear watery stools. Bowel preparation was not used in patients with third-degree extensions. Repairs were performed under regional anesthesia, using a layered closure with either chromic catgut or Vicryl. When there was repair of a fourth-degree extension, patients were given a low-residue diet for 1 to 3 days; patients with third-degree extensions were placed on a regular diet. Otherwise, postoperative care consisted of sitz baths three to four times daily and heat lamps for drying. Follow-up care after discharge was in 1 week (27). The average time from delivery to discharge after repair was 15.5 days.

Necrotizing Fasciitis

In necrotizing fasciitis of an episiotomy (25,26,27,28 and 29,31), both layers of the superficial perineal fascia become necrotic, and infection spreads along the fascial planes to the abdominal wall, thigh, or buttock. Typically, the deep perineal fascia (i.e., inferior fascia of the urogenital diaphragm) is not involved. Skin findings vary, but initially include edema and erythema without clear borders. Later there is progressive, brawny edema of the skin. The skin becomes blue or brown, and bullae or frank gangrene may occur. As the infection progresses, there may be loss of sensation or hyperesthesia (Fig. 21.12).

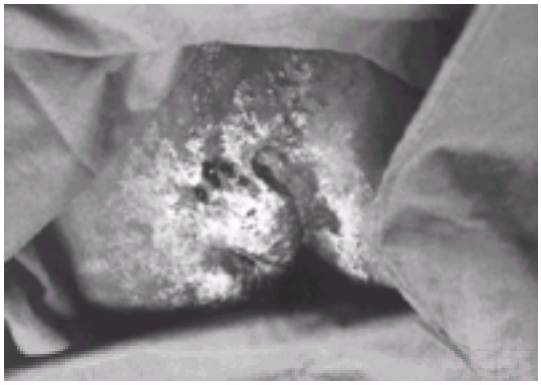


FIGURE 21.12. Puerperal necrotizing fasciitis of the left vulva following delivery and episiotomy. Note involvement of the buttocks, thighs, and mons. (Courtesy of Dr.

James A. McGregor, University of Colorado Health Sciences Center, CO, USA.)

Associated findings upon admission include marked hemoconcentration, although after fluid replacement the patient often is anemic. Hypocalcemia may develop due to saponification of fatty acids. Traditionally, this infection has been associated with group A streptococci, but more recent publications indicate that anaerobic bacteria also play important roles.

Effective therapy requires prompt, adequate debridement. Surgical exploration usually is indicated by (a) extension beyond the labia, (b) unilateral edema, (c) systemic signs of toxicity or deterioration, and (d) failure of the infection to resolve within 24 to 48 hours (Box 2).

Box 2

Episiotomy Infections

Surgical exploration of episiotomy infections usually is indicated by

- Extension beyond the labia, or
- Unilateral edema, or
- Systemic signs of toxicity or deterioration, or
- Failure of infection to resolve within 24 to 48 hours

At surgery, necrotizing fasciitis can be recognized by separation of the skin from the deep fascia (by blunt dissection with a finger or Kelly clamp), absence of bleeding along incision lines, and a serosanguinous discharge. Dissection should be carried out until all necrotic tissue is debrided.

Myonecrosis

Myonecrosis involves the muscles beneath the deep fascia (20). Often, this is caused by myotoxin from *C. perfringens,* but occasionally it may result from an extension of necrotizing fasciitis. Onset may be early and typically is accompanied by severe pain and often by disorientation and shock. Treatment is extensive debridement and high-dose antibiotics including penicillin when clostridial species are suspected.

Differential Diagnosis

Not all puerperal vulvar edema signifies perineal infection (Fig. 21.13) In most cases, vulvar edema results from a less serious cause, such as vulvar hematoma, prolonged bearing down in labor, generalized edema from toxemia, allergic reactions, and trauma without serious infection. With these disorders, edema usually is bilateral, does not extend to the buttock and abdominal wall, and is not

accompanied by signs of toxicity.

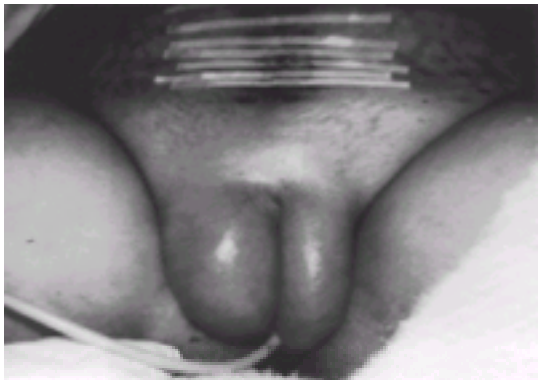


FIGURE 21.13. Vulvar edema of a noninfectious source. This patient had generalized edema from nephrotic syndrome with superimposed preeclampsia. Edema is bilateral and does not extend to the buttocks or abdominal wall.

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22

PARASITIC DISEASE IN PREGNANCY

Parasitic infections have a worldwide distribution, and significant parasitic infestations occur during pregnancy (1). These infections include diseases due to protozoa or helminths. Such agents are generally more common in tropical and underdeveloped areas of the world. The worldwide public health impact of protozoan and helmintic infections is significant. The protozoan organisms *Plasmodium* sp (malaria), *Entamoeba histolytica*, *Trypanosoma* sp, and *Leishmania* sp are major causes of disease and mortality in Africa, Asia, and Central and South America (1). Other protozoa, such as *Giardia lamblia* and *Cryptosporidium,* frequently cause diarrheal disease in both developing and industrialized countries. With the spread of human immunodeficiency virus (HIV) infection, other protozoa, such as *Pneumocystis carinii, Toxoplasma gondii,* and *Cryptosporidium,* have taken on greater importance. It has been suggested that helminths are the most prevalent infectious agents in humans (2). *Ascaris, Trichuris,* and the hookworms account for nearly one billion infections each; the schistosomes and filariae account for 250 million infections each. In 1988, Walsh (3) estimated that over 2.2 million deaths occurred annually as the result of parasitic diseases in developing countries (Table 22.1). The range of protozoans and helminths that infest humans is vast. Table 22.2 lists the infestations that either are common or have a potentially adverse effect on pregnancy outcome. Although the prevalence of parasitic diseases during pregnancy is much lower in the United States and other western industrialized nations, the wide accessibility to rapid foreign travel has resulted in a rather large “at risk” pool of tourists exposed to a multitude of protozoan and helmintic infections during their travels. Ironically, the response to parasitic infection by nonresident visitors to endemic areas may be more severe than that of the local inhabitants who have acquired immunity to these agents. The recent influx of immigrants to the United States from South and Central America and Southeast Asia has led to the presence of a population with a very high prevalence of parasitic infestation. In addition, the

use of immunosuppressive drugs and the spread of HIV infection has led to an increased prevalence of infections caused by a variety of parasites. Finally, there are areas in the United States where the environmental, economic, and sanitary conditions are appropriate for the maintenance of endemic parasites (2). Epidemics of giardiasis and amebiasis have occurred in the United States, schistosomiasis is endemic in Puerto Rico, and hookworm is endemic in the Southeastern United States. *Entamoeba histolytica* is a frequent cause of diarrhea in homosexual men with acquired immunodeficiency syndrome (AIDS).

Disease	Deaths/Year
Malaria	1,500,000
Schistosomiasis	500,000
Amoebiasis	70,000
Chagas disease	60,000
Hookworm	50,000
Ascariasis	10,000
Giardiasis	10,000
Leishmaniasis	1,000
Trichuriasis	1,000
Filariasis	1,000
Total	2,203,000

TABLE 22.1. DEATHS DUE TO PARASITIC DISEASES IN DEVELOPING COUNTRIES

Protozoan agents	
Entamoeba histolytica	*Leishmania donovani*
Giardia lamblia	*Leishmania major*
Cryptosporidium	*Leishmania tropica*
Plasmodium falciparum	*Leishmania aethiopica*
Plasmodium vivax	*Leishmania mexicana*
Plasmodium malariae	*Leishmania Vienna group*
Plasmodium ovale	*Trypanosoma cruzi*
Trichomonas vaginalis	*Trypanosoma gambiense*
Pneumocystis carinii	*Trypanosoma rhodesiense*
	Toxoplasma gondii
	Babesia sp
Helminths	
Intestinal nematodes (roundworms)	Trematodes (flukes)
Ascaris lumbricoides	*Schistosoma mansoni*
Trichuris trichiura	*Schistosoma japonicum*
Enterobius vermicularis	*Schistosoma haematobium*
Ancylostoma duodenale	*Schistosoma mekongi*
Necator americanus	*Schistosoma intercalatum*
Strongyloides stercoralis	Cestodes (tapeworms)
Tissue nematodes	*Taenia saginata*
Trichinella spiralis	*Taenia solium*
Wuchereria bancrofti	*Diphyllobothrium latum*
Brugia malayi	*Hymenolepis nana*
	Echinococcus granulosis

TABLE 22.2. PARASITIC INFESTATIONS THAT CAN OCCUR IN PREGNANT WOMEN

Lee (4) has suggested that parasitic infestation may adversely affect fertility and/or reproductive capacity in three ways (Table 22.3). First, the infecting organism can result in sufficient debilitation and/or anatomic damage to the genital tract so that either conception is impossible or normal implantation does not occur. Second, parasitic infestations may be severe enough to adversely affect the mother's health to the point where medical intervention to terminate the pregnancy is required. Third,

protozoan parasites may infect and cross the placenta to produce adverse fetal effects, such as abortion, fetal infection, stillbirth, intrauterine growth retardation (IUGR), and congenital infection. Additional mechanisms for producing adverse effects on pregnancy outcome have been proposed (5). The nutritional status of pregnant women in the tropics and underdeveloped areas is borderline. Parasitic disease may interfere significantly with the nutrition of these women and may result in a worsening of the already critical nutritional status with resultant impaired fetal growth. Another factor leading to poor outcome may be that malnutrition is associated with immunodeficiency; thus, the susceptibility of pregnant women to bacterial and viral infections and their recognized consequences for the fetus and newborn is increased.

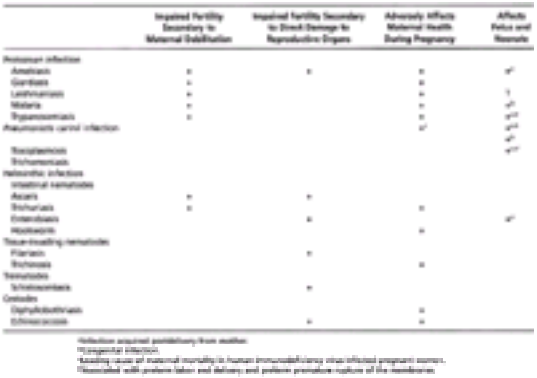


TABLE 22.3. ADVERSE EFFECT OF PARASITIC DISEASES ON FERTILITY AND PREGNANCY OUTCOME

In general, the majority of parasitic infections that occur in pregnancy without HIV infection do not require treatment during pregnancy. Although Roberts et al. (6) identified gastrointestinal parasites in 65% of Southeast Asian refugees, they noted no significant differences in maternal weight gain, hemoglobin levels, gestational age at delivery, birthweight, or neonatal morbidity rates among pregnant women with or women without colonization with intestinal parasites. However, if severe symptoms, anemia, and/or malabsorption occur, treatment should be initiated during pregnancy. As discussed later, certain parasitic infections should always be treated during pregnancy. These infections include symptomatic amebiasis, severe giardiasis, malaria, and ascariasis. Moreover, parasitic infections associated with HIV infection, such as *P. carinii* and *T. gondii,* should be treated aggressively.

Because of the levels of worldwide travel, immigration patterns, and spread of HIV infection, health care providers should be cognizant of protozoan and helmintic infections. As described by Ravdin (1), the key to recognizing these infections includes knowledge of epidemiologic risk factors, geographic distribution, and clinical presentation. In addition, diagnosis and treatment require use of tests and drugs that are unfamiliar to most physicians in the United States. These issues will be discussed in the remainder of this chapter.

PROTOZOAN INFECTIONS

Amebiasis

Amebiasis is an ulcerative and inflammatory disease of the colon caused by the protozoan *E. histolytica*. The organism can occur in extraintestinal sites, most commonly the liver, where severe tissue damage can occur (1,2). Amebiasis occurs throughout the world; its prevalence is highest in tropical areas and countries with low levels of sanitation and personal hygiene (1,2 and 3). Analysis of zymodemes (patterns of electrophoretic mobility of parasites isoenzymes) and molecular biology tools have produced evidence confirming the presence of distinct pathogenic and nonpathogenic strains of *Entamoeba* that are morphologically identical (1,2). *Entamoeba dispar* is the most prevalent species, but it is only associated with an asymptomatic carrier state (2). *Entamoeba histolytica* is the pathogenic strain that can invade tissue and produce symptomatic disease (2). Walsh (4) estimated that more than 10% of the world's population is infected by *E. dispar* and *E. histolytica.* Nearly 50% of the population is infected in many developing countries.

Each year in the world (excluding the People's Republic of China), there are approximately 50 million cases of symptomatic diseases, with an estimated 100,000 deaths (4). In the United States, the overall prevalence of *Entamoeba* infection is estimated to be 3% to 4% (1,2). A high incidence of infection is present in certain high-risk groups (e.g., institutionalized populations, sexually promiscuous male homosexuals, and recent immigrants or migrant workers from *E. histolytica* endemic areas) (1). *Entamoeba histolytica* is the third most common cause of death due to parasitic infections in developing nations and a major health risk to travelers to these areas (4). *Entamoeba histolytica* is not transmitted across the placenta and thus does not have a direct effect on the fetus. However, it can produce severe maternal disease during pregnancy or in association with malnutrition (5,6).

Infection is acquired by ingestion of the cyst form of *E. histolytica* in food or water contaminated by feces. Direct fecal-oral contact also transmits the cyst form. The cysts, which contain eight trophozoites, rupture in the small bowel to release the trophozoites. The trophozoites migrate to the colon, where binary fission occurs every 8 hours. If environmental conditions are not appropriate for continued multiplication, encystment occurs, and the life cycle is complete (2). Following encystment of a trophozoite, the cysts are excreted in feces and can survive for weeks in an appropriate moist environment. However, the trophozoite, under the influence of poorly understood environmental factors, may invade the mucosal wall of the colon (7). The trophozoites are facultative anaerobes. Once they gain access to submucosal areas, they are capable of maintaining an ideal environment for their survival by producing tissue anoxia, necrosis, and a low pH. It is this large area of necrosis in the submucosa that produces the characteristic flask-shaped ulcer of amebiasis. Hepatic infection occurs when trophozoites ascend in the portal venous system and produce hepatic necrosis secondary to obstruction of portal vessels (1). Ravdin (8) has described both the epidemiologic risk factors for acquiring *E. histolytica* and the occurrence of severe disease (Table 22.4).

Prevalence	Increased Severity
Lower socioeconomic status in an endemic area, including crowding and lack of indoor plumbing	Children, especially neonates
	Pregnancy
Immigrants from endemic area	Corticosteroid use
Institutionalized individuals, especially those who are mentally retarded	Malignancy
Communal living	Malnutrition
Promiscuous male homosexuals	Human immunodeficiency virus infection

Modified from Ravdin (8).

TABLE 22.4. EPIDEMIOLOGIC RISK FACTORS ASSOCIATED WITH *ENTAMOEBA HISTOLYTICA* INFECTION AND INCREASED SEVERITY OF DISEASE

Clinical Presentation

Clinical findings associated with *E. histolytica* infestation range from the asymptomatic carrier state to fulminant dysentery (Table 22.4). The asymptomatic state is the most common manifestation of this infection. All *E. dispar* infections and up to 90% of *E. histolytica* infections are asymptomatic (1). It has been estimated that clinical disease may occur in 10% to 50% of asymptomatic carriers (5). Immunosuppression, malnutrition, steroid therapy, and pregnancy have been noted to result in the development of clinical disease in asymptomatic carriers (5,6).

Clinical amebiasis may be mild (noninvasive disease) and characterized by colonic irritation with colicky lower abdominal pain and increased frequency of bowel movements; stool may be loose, with mucus and/or blood present. With more extensive colonic disease (invasive), the patient presents with bloody frequent diarrhea stools, abdominal pain and tenderness, right upper quadrant pain and tenderness, and hepatomegaly. Acute amebic rectocolitis (dysentery) is characterized by gradual onset over 1 to 3 weeks, abdominal pain, diarrhea, dysentery, weight loss, fever (one third of cases), abdominal tenderness, and heme-positive stools. The reported case fatality rate ranges from 1.9% to 9.1% (9,10). Juniper (10) reported that the case fatality rate in women was twice the rate in males. Fulminant colitis is an infrequent but highly lethal form of amebic infection (1,11). It has a predilection for malnourished individuals, pregnant women, patients taking corticosteroids, and young infants (1). These patients present with severe illness characterized by fever, leukocytosis, profuse bloody mucoid diarrhea, diffuse abdominal pain, and often hypotension with signs of peritonitis following transmural necrosis of the bowel. In the extreme, an acute abdomen can be present secondary to bowel perforation and acute amebic peritonitis following transmural necrosis of the bowel. This serious complication occurs in 3% to 4% of patients with severe amebic dysentery and is associated with a high mortality rate (1,2,9).

Toxic megacolon is an uncommon complication of acute amebic colitis associated with inappropriate use of corticosteroids (1,12). Because toxic megacolon does not respond to medical therapy and requires colectomy, its recognition is critically

important (2). Ameboma presents as an annular lesion of the colon that is difficult to differentiate from colon carcinoma. In endemic areas, serologic testing for antiamebic antibodies or colonoscopy-directed biopsies should be performed prior to surgical exploration (2). Following an acute episode of amebiasis, a chronic irritative bowel syndrome may persist for several months but usually resolves spontaneously.

In addition to peritonitis secondary to bowel perforation, extraintestinal amebiasis may occur by metastasis of trophozoites via the portal vein system of lymphatics, usually to the liver initially. The majority of patients with amebic liver abscesses have no history of antecedent or current bowel disease (1,8). Patients with amebic liver abscess present with acute onset (<10 days) of right upper quadrant pain, fever, tender hepatomegaly, rapid weight loss, and pallor. Alternatively, liver abscess may present subacutely with weight loss as the most prominent finding; less than 50% of patients have fever or abdominal pain (2). Amebic liver abscesses may extend into adjacent organs, most commonly the pleural cavity, but rupture into the pericardium or peritoneum may occur (1,2,13).

The most common complication of amebic liver abscess is pleuropulmonary amebiasis secondary to rupture of the abscess into the pleural cavity (2). This entity presents with cough, pleuritic pain, and dyspnea (2,14). Empyema resulting from rupture of a liver abscess into the pleural cavity presents more dramatically with sudden respiratory distress and pain and is associated with a high mortality rate of 15% to 35% (2,14). Cerebral amebiasis is a rare cause of brain abscess. However, its onset is abrupt, with rapid progression to death within 12 to 72 hours unless appropriate therapy is commenced (1,2). Genitourinary amebiasis is very rare; it is found in association with rectovaginal fistulas that allow spread of *E. histolytica* trophozoites to the genital tract (2,15,16). Genitourinary amebiasis presents as painful granulation tissue or ulcers mimicking malignancy.

Diagnosis

The diagnosis of intestinal amebiasis is made by demonstrating *E. histolytica* or *E. dispar* in the stool. The presence of either trophozoites or cysts confirms the diagnosis (Fig. 22.1 and Fig. 22.2). Stool specimens are best examined fresh. Fresh stool specimens should be smeared and stained with iron hematoxylin or Wheatly trichrome stain or fixed in polyvinyl alcohol for later evaluation (2). This approach facilitates the ability to identify hematophagous (erythrocyte-containing) trophozoites, which differentiates *E. histolytica* from *E. dispar,* and is the characteristic sign of invasive colonic disease (1,2). Examination of a single stool specimen identifies only one third of infected patients; thus, three specimens should be assessed before excluding the diagnosis of amebiasis. Although stool cultures for *E. histolytica* are more sensitive, usually they are not clinically available. Endoscopy is an excellent approach for making the diagnosis. Amebic colitis appears as punctuate hemorrhagic areas or small ulcers with exudative centers and hyperemic borders. Aspiration of these lesions provides a reliable specimen for identification of motile, erythrocyte-containing trophozoites of *E. histolytica*.

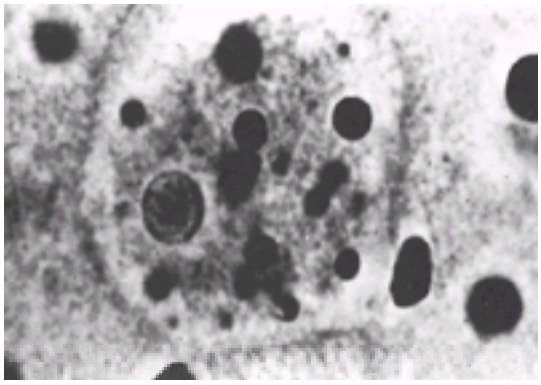


FIGURE 22.1. Trophozoites of *E. histolytica*. A delicate round nucleus is seen and the trophozoite contains ingested red blood cells. (From Ravdin JI, Petri WA Jr. Entamoeba histolytica (amebiasis). In: Mandel GL, Douglas RG, Bennett JE, eds. *Principles and practice of infectious diseases*. New York: John Wiley & Sons, 1990, with permission.)

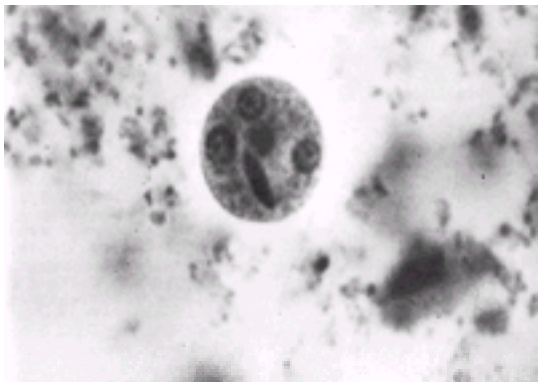


FIGURE 22.2. Mature cyst of *E. histolytica* with three of four nuclei seen. (From Ravdin JI, Petri WA Jr. Entamoeba histolytica (amebiasis). In: Mandel GL, Douglas RG, Bennett JE, eds. *Principles and practice of infectious diseases*. New York: John Wiley & Sons, 1990, with permission.)

Serum antiamebic antibody tests have been shown to be useful in the diagnosis of invasive intestinal amebiasis (2,17,18). Result of these serologic tests are negative in patients infected with *E. dispar,* and serum antibodies to amoebae only occur with *E. istolytica* infection. Promising new methods for diagnosis of infection with *E. histolytica* include antibodies against purified parasite antigens and direct detection of *E. histolytica* antigen in serum or feces (2).

Patients with amebic liver abscess often do not have concurrent intestinal involvement; thus, stool specimens are negative for *E. histolytica*. Diagnosis of amebic liver abscess relies on recognition of the clinical manifestations and epidemiologic risk factors; noninvasive imaging studies demonstrating a solitary

(usually) defect in the right lobe of the liver; and detection of serum antiamebic antibodies (indirect hemagglutination). Imaging techniques include ultrasound, computed tomographic scan, magnetic resonance imaging, technetium liver scan, and gallium scan. None is specific for amebic liver abscess. Ultrasound is rapid and less costly and thus should be the initial imaging technique. In general, aspiration of the cyst is not necessary to make the diagnosis. However, in cases where the patients are too ill to await serologic results, liver aspiration under computed tomographic or ultrasound guidance should be performed (2). With amebic abscess, the aspirate contains no white blood cells, is odorless, and brown or yellow liquid is present. Amebas are not seen in most cases, as they tend to be in the wall of the abscess (2).

Effects of Amebiasis on Pregnancy

Several reports have suggested that amebiasis during pregnancy may be more severe and may be associated with a higher mortality rate than occurs in nonpregnant women (5,19,20). Abioye (20) 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. Reinhardt (6) described several factors that may account for this increased susceptibility during pregnancy. These factors included (a) increased levels of free plasma cortisol during pregnancy; (b) increased levels of serum cholesterol in early pregnancy; and (c) malnutrition and anemia, which are commonly present in pregnant women living in areas endemic for amebiasis. It also has been suggested that amebiasis during pregnancy may result in an adverse effect on the fetus (21). Czeizel et al. (21) noted that women with spontaneous abortions had a significantly higher incidence of positive stool cultures for *E. histolytica* compared with women having term births. In addition, they demonstrated an increased incidence of amebiasis in women with stillbirths, preterm deliveries, and infants having congenital anomalies than in women with normal term deliveries. It is important to recognize that asymptomatic or mild amebiasis may develop into severe amebic dysentery during pregnancy and the puerperium. Thus, consideration must be given to treatment of these milder forms of amebiasis in pregnant women.

There is no evidence that *E. histolytica* is associated with intrauterine fetal infection. However, the newborn may acquire the disease secondary to person-to-person transmission, usually from its mother. Neonates with amebiasis present with sudden onset and are seriously ill with bloody diarrhea, hepatic abscess, gangrene of the colon, and colon perforation with peritonitis (22).

Treatment

Treatment of *E. dispar* infection is not recommended (2). On the other hand, it is recommended that even asymptomatic infection with *E. histolytica* be treated. Because the cyst stage of *E. histolytica* is resistant to physical and chemical agents, antimicrobial therapy is directed against the trophozoite stage. A variety of drugs are available, and the treatment regimen should be based on both the location (intraluminal, intestinal [submucosa and/or extraintestional]) and severity of amebiasis (1,2). In addition, it is very important that pregnant women with amebiasis be treated during pregnancy because of the reported increased incidence of severe disease in pregnancy (19,20).

Table 22.5 summarizes the recommendations for treatment of amebiasis (1,2,23,24). In asymptomatic intraluminal infection, the drug of choice in nonpregnant patients is diloxanide furoate (Furamide) 500 mg three times a day for 10 days (available through Centers for Disease Control and Prevention). Paromomycin (Humatin) 30 mg/kg/day in three divided doses for 5 to 10 days also is effective for intraluminal disease. Paromomycin has the advantage of being nonabsorbable. Diiodohydroxyquin (iodoquinol) is in limited supply in the United States. Because the effects of diloxanide furoate on pregnancy are unclear, this drug generally is not used for asymptomatic amebiasis during pregnancy. Thus, paromomycin (Humatin) is the drug of choice for asymptomatic disease in pregnancy (Table 22.5). In pregnant asymptomatic patients, metronidazole 750 mg three times a day for 10 days is an alternative choice.

TABLE 22.5. RECOMMENDED THERAPY FOR COMMON PROTOZOAN INFECTIONS

Symptomatic intestinal amebiasis requires treatment with an agent active against trophozoites invading the colon wall, followed by an agent able to eradicate intraluminal encysted *E. histolytica*. For symptomatic intestinal disease, the drug of choice is metronidazole 750 mg three times a day for 5 to 10 days, followed by diloxanide furoate (Furamide; available through CDC) or paromomycin (Humatin). If nausea and abdominal discomfort occur with this dose of metronidazole, a regimen of 2.4 g/day for 2 days also is effective (2). Alternatively, with mild colitis in patients unable to tolerate metronidazole, tetracycline 250 mg orally four times a day for 15 days is effective in combination with an intraluminal agent. However, these combination regimens will not eradicate trophozoites in the liver (1). Some experts recommend adding chloroquine to the tetracycline approach, but others suggest careful follow-up of patients treated with tetracycline for evidence of hepatic involvement (1,2). Alternate regimens for severe intestinal disease include dehydroemetine 1 to 1.5 mg/kg/day intramuscularly or subcutaneously for 5 days (maximum dose 90 mg/day), followed by diloxanide furoate (Furamide) or paromomycin (Humatin). Because of cardiac toxicity, emetines are generally limited to situations of a critical nature, such as amebic peritonitis or ruptured amebic abscess. Other major side effects include gastrointestinal toxicity in up to 50% of patients and neuromuscular complaints (1). In pregnancy, the regimen of choice for

symptomatic intestinal disease is metronidazole plus paromomycin (Humatin) (Table 22.5). The current consensus is that metronidazole is safe to use in pregnancy; no teratogenic effect has been documented.

The regimen of choice in amebic hepatic abscess and other extraintestinal disease is metronidazole, followed by an agent to prevent continued intraluminal infection and diloxanide furoate (Furamide) or paromomycin (Humatin) in doses similar to that for severe intestinal disease (1,2,24). Alternative regimens consist of dehydroemetine 1 to 1.5 mg/kg/day intramuscularly (maximum 90 mg/day) for up to 5 days, followed by diloxanide furoate (Furamide), paromomycin (Humatin), or chloroquine phosphate 600 mg base (1 g) per day for 2 days, then 300 mg base (500 mg per day for 2 to 3 weeks. In patients with serious complications such as a ruptured amebic abscess or peritonitis, parenteral emetine 65 mg once a day for the initial 2 or 3 days should be given. This provides rapid amebicidal action but limits the risk of cardiotoxicity with this agent. In pregnancy, the regimen of choice is metronidazole plus diloxanide furoate (Furamide) or paromomycin (Humatin) (Table 22.5).

Giardiasis

Giardia lamblia is a flagellated protozoan parasite that has a cystic stage that infects the host and a motile trophozoite stage that produces disease (1,2). It is a major cause of endemic and epidemic diarrhea. Giardiasis is a ubiquitous disease with worldwide distribution. The incidence of *Giardia* is higher in developing countries where poverty, poor sanitation, lack of medical care, and overcrowding facilitate the spread and persistence of the organism (2). Areas of increased risk include Southeast and South Asia, West and Central Africa, South America, Mexico, Korea, and the Soviet Union. In addition, large-scale epidemics of giardiasis have occurred in the United States (3,4). Waterborne outbreaks of giardiasis frequently occur in mountainous areas of the northeast, northwest, and Rocky Mountain states in the United States. These outbreaks are generally due to faulty purification systems or untreated water in wilderness areas (5,6). *Giardia lamblia* is the most commonly identified pathogenic intestinal parasite in the United States, occurring in 3% to 9% of stool specimens (1,2,7,8 and 9).

The resistant cyst stage is transmitted by the fecal-oral route; thus, acquisition of *G. lamblia* requires oral ingestion of fecally contaminated water. Person-to-person transmission is frequent in daycare centers and among male homosexuals. With exposure to the acidic pH of the stomach, the cysts rupture to release trophozoites. The trophozoites multiply rapidly in the small bowel and firmly attach via their suckling disc to the intestinal epithelium. The mechanism for the diarrhea and malabsorption has not been elucidated. The cysts develop as liquid feces is dehydrated during transit through the colon. The exact mechanisms that induce cyst formation are not known.

Clinical Presentation

P>Giardiasis may range from an asymptomatic carrier state to severe diarrhea with malabsorption. As described by Hill (1), 5% to 15% of persons ingesting *G. lamblia* become asymptomatic cyst passers, 25% to 50% become symptomatic with an acute diarrheal syndrome, and 35% to 70% do not have any signs or symptoms of infection. Characteristically, giardiasis presents with sudden onset of explosive, watery, foul-smelling, bulky diarrhea. Anorexia, nausea, vomiting, belching of sulfuric

material, abdominal cramps, low-grade fever, chills, and malaise also occur. There is an absence of blood, mucus, or polymorphonuclear cells in the stool. Most cases last for several weeks. In most instances, giardiasis runs a relatively benign course (1). However, children younger than 5 years old and pregnant women may present with severe illness and hypovolemia requiring hospitalization (1,10).

Diagnosis

It is important to consider a diagnosis of giardiasis in any patient presenting with prolonged diarrhea, especially when associated with weight loss or malabsorption (1). In the early acute stage, giardiasis can be diagnosed by immediate examination of a stool wet smear, which demonstrates trophozoites. Alternately, stool can be preserved in formalin or polyvinyl alcohol for later examination. Later in the disease process, the stool is more formed and contains the cyst form. Concentration techniques usually are necessary to demonstrate these cysts. Commercially available tests for detection of *Giardia* antigen in the stool recently have become available. These tests have a sensitivity of 85% to 98% and a specificity of 90% to 100%. These tests are superior to stool examination for ova and parasites (11), including detection of *Giardia* antigen by immunofluorescence on enzyme-linked absorbent assay (ELISA) (12,13). In most circumstances, stool examination or an antigen assay is sufficient to diagnose *Giardia*. However, in difficult cases, diagnosis of a sampling of duodenal contents by aspiration or biopsy may be required (1). Duodenal aspirates will contain motile trophozoites. The string test or Entero-Test (HDC Corp., San Jose, CA, USA) is the easiest to perform. Whereas immunoglobulin G (IgG) antibody against *Giardia* remains elevated for long periods of time, anti-*Giardia* immunoglobulin M (IgM0 can be used to differentiate current from previous infection.

Effect on Pregnancy

In general, giardiasis has minimal adverse effects on pregnancy outcome (4). However, significant malabsorption may impair fertility and adversely affect pregnancy. Kreutner et al. (7) described three cases of severe giardiasis in pregnant women and suggested that the disease is more severe in pregnancy with significant weight loss and debility.

Treatment

The drug of choice for giardiasis is metronidazole 250 mg three times a day for 5 to 7 days (1,11,14). Quinacrine also is effective but has not been available in the United States since 1992. If quinacrine can be obtained, the dosage is 100 mg three times a day for 5 to 7 days. Alternative agents include furazolidone (Furoxone) 100 mg four times a day for 7 to10 days and paromomycin (Humatin) 25 to 30 mg/kg/day in divided doses three times per day for 5 to 10 days (1,11,14). Tinidazole, another nitroimidazole not available in the United States, is very effective against *Giardia* as a single 2-g dose (15). Mebendazole (Vermox) is safe in pregnancy but limited data have not been encouraging (1). Because of concerns that these drugs may adversely affect the fetus, the recommended treatment of symptomatic giardiasis in pregnancy previously consisted of paromomycin (Humatin) (25–30 mg/kg/day in divided doses three times a day for 5–10 days) (11,14). However, recent consensus is that metronidazole is safe to use in pregnancy, even during the first trimester (16,17); thus, metronidazole can be used safely in pregnancy in doses similar to

doses recommended for nonpregnant individuals. When the disease is mild, therapy can be delayed until after delivery or, in the case of metronidazole, until after the first trimester.

Leishmaniasis

Leishmaniasis is a group of clinical diseases produced by protozoan organisms of the genus *Leishmania* (1,3 and 4). It is endemic in many subtropical regions of the world (2). Leishmaniasis has grown in importance because of the widespread accessibility of international travel and the AIDS epidemic (2).

Leishmanias exists as intracellular amastigotes in macrophages in humans and other mammalian hosts and as extracellular promastigotes in the gut of their sandfly hosts (1,2). The six major species and their subspecies that are human pathogens are listed in Table 22.6. These various species of *Leishmania* are transmitted by the bite of infected female sandflies, mostly *Phlebotomus, Lutzomyia,* and *Phychodophgus* (5). A single species of *Leishmania* can present as different clinical syndromes, and each syndrome can be caused by more than one species (1). Other than New World cutaneous leishmaniasis, where differentiating *Leishmania mexicana* from *Leishmania (Viannia)* group has treatment implications, recognition of the clinical forms of leishmaniasis is the key to appropriate therapy.

TABLE 22.6. *LEISHMANIA* SPECIES: ASSOCIATED CLINICAL SYNDROMES AND GEOGRAPHIC DISTRIBUTION

Leishmaniasis presents clinically in four distinct forms (4). Kala azar (visceral or systemic leishmaniasis) usually is caused by *Leishmania donovani, Leishmania infantum,* or *Leishmania chagasi.* Cutaneous leishmaniasis (oriental sores) in the Old World is produced by *Leishmania tropica, Leishmania aethiopica,* and *Leishmania major.* When widespread cutaneous papules or nodules are present all over the body, the condition is labeled “diffuse cutaneous leishmaniasis” (4). American leishmaniasis (mucocutaneous disease) is due to *L. mexicana* and *Leishmania (Viannia)* group. The *Leishmania (Viannia) braziliensis* complex is responsible for mucosal disease in the Americas.

Kala azar is widely distributed throughout the world; its greatest prevalence is in India, Bangladesh, and China (1). Cutaneous leishmaniasis (Oriental sores) occurs in tropical and subtropical areas of the eastern and western hemispheres, especially China, Asia Minor, Africa, and Central and South America. The mucocutaneous form of the disease is seen in Central and South America. In 1994, there were an estimated 1 to 1.5 million cases of cutaneous leishmaniasis and 500,000 cases of visceral leishmaniasis per year (6).

Clinical Presentation

Visceral leishmaniasis (kala azar) has a slow insidious onset following an incubation period of 3 to 8 months (1,2,3 and 4). It characteristically presents as prolonged fever, progressive weight loss, weakness, hepatosplenomegaly, anemia, leukopenia, hypoalbuminemia, and hyperglobulinemia. As the disease progresses, the skin becomes grayish in color. It is this discoloration that led to the name kala azar, which is the Indian word for “black fever”. Untreated visceral leishmaniasis may be fatal. This form of leishmaniasis is an important opportunistic infection in persons with HIV infection in Spain, France, and Italy (1).

Old World cutaneous leishmaniasis has an incubation period ranging from 2 weeks to several months. With *L. tropica* (urban or dry form), the lesions are single, grow slowly, and persist for 1 year or more. In disease due to *L. major and L. braziliensis* (rural or moist form), lesions may be multiple, have a granulating base, grow rapidly, and heal within several months (1). Cutaneous leishmaniasis initially appears as a pruritic red papule that occurs at the site of inoculation. This lesion slowly progresses to a shallow ulcer with seropurulent discharge. Tender regional lymphadenopathy is present. The ulcer generally heals spontaneously over several months. Diffuse cutaneous leishmaniasis begins as a localized papule but does not ulcerate. Rather, satellite lesions develop and organisms spread to distant sites on the skin, especially the face and extremities. This form progresses very slowly and can persist for 20 years or more.

In American cutaneous leishmaniasis, the incubation time is 2 to 8 weeks. A wide variety of skin lesions may present, ranging from small dry, crusted lesions to large mutilating ulcers. Lesions may be single or multiple and occur primarily on exposed areas of the body. *Leishmania braziliensis* can persist after resolution of the primary cutaneous ulcer and result in a mutilating infection involving mucosal areas.

Although the mucocutaneous form of leishmaniasis begins similarly as a small papule that progresses to an ulcerative stage, this disease is progressive in nature, with development of new ulcerations involving the mucocutaneous borders of the nose and mouth (1). Initial symptoms include nasal congestion, discharge, discomfort, or epistaxis (1). Extensive tissue destruction and scarring occur, as these lesions slowly heal over several years. The nasal septum may be destroyed, leading to nasal collapse, or perforation can occur through the soft palate. Involvement of the genital mucosa has been reported (1).

Diagnosis

Diagnosis of leishmaniasis may be difficult due to the various forms of the disease,

the number of *Leishmania* sp involved, geographic variations, and other syndromes with similar clinical manifestations (e.g., yaws, cutaneous tuberculosis, blastomycosis) (4). Diagnosis of leishmaniasis should always be considered in known endemic areas of the world (3). Unfortunately, in the United States the diagnosis often is delayed or missed in immigrants or returning international travelers (3). Indigenous cutaneous leishmaniasis occurs in the United States in a region of southern Texas extending from San Antonio to the Mexican border (7).

The gold standard for diagnosis of leishmaniasis is the isolation or identification of the causative parasite from infected sites (1,2,5). The diagnosis of visceral leishmaniasis (kala azar) is suggested by the characteristic clinical presentation occurring in an endemic area and is confirmed by demonstrating leishmania bodies within cells of the reticuloendothelial system, usually by marrow aspiration or splenic aspiration. Splenic aspiration is the most sensitive diagnostic method, but life-threatening hemorrhage has complicated this technique (1). Although bone marrow aspiration is less sensitive, it is safer. Culture can be performed on this specimen. In addition, a slide smear (Wright-Giemsa) can be examined for the presence of *Leishmania* organisms. After *Leishmania* has been isolated in culture or identified in tissue, a variety of techniques are available for specification (5), including isoenzyme analysis, specific monoclonal antibodies, and DNA hybridization with or without polymerase chain reaction (PCR). In immunocompetent persons, antileishmanial antibodies usually are present in high titers with the use of ELISA, indirect immunofluorescence assay, or direct agglutination test (1). Among HIV-infected patients, antileishmanial antibodies usually are absent or present in low titers (1).

Cutaneous leishmaniasis is suspected when the typical ulcer appears in an endemic area. The diagnosis is confirmed by demonstrating the organism (amastigotes) in smears or promastigotes in cultures obtained from the borders of the lesion. The Montenegro skin test becomes positive during the course of this form of leishmaniasis. Antileishmanial antibodies may be present in some patients with cutaneous leishmaniasis, but the titers usually are low (1).

Mucosal leishmaniasis is diagnosed definitively by identifying amastigotes in touch preparations or tissue specimens or isolating promastigotes in culture (1). The causative agent of mucosal disease, *L. (V.) braziliensis,* is difficult to grow and the parasite burden is low (1). Thus, the diagnosis often is made presumptively based on the clinical findings, a characteristic scar evidencing prior skin infection, and either a positive *Leishmania* skin test (Montenegro) or presence of antileishmanial antibodies (1, 2).

The development of fever and hepatosplenomegaly up to 2 years after visiting an endemic area suggests the possibility of kala azar. Similarly, cutaneous leishmaniasis is suggested by the appearance of indolent ulcerations occurring on exposed skin within months of travel in an endemic area (1).

Effect On Pregnancy

Visceral leishmaniasis (kala azar), caused by *L. donovani*, is the only form of leishmaniasis in which a parasitemia occurs (8,9). Consequently, it is the only leishmaniasis reported to cause intrauterine fetal infection (9). If visceral leishmaniasis (kala azar) is acquired during pregnancy, Lee (8) has suggested that it

is associated with increased fetal loss.

Treatment

Treatment of leishmaniasis traditionally has relied on the use of pentavalent antimony-containing compounds (Table 22.5) However, increasing drug resistance and treatment failures, failure of immunocompromised patients to respond, and frequent side effects are associated with use of these agents. Recently, liposomal amphotericin B became the first drug licensed by the U.S. Food and Drug Administration (FDA) for treatment of visceral leishmaniasis (1). Alternatives include pentamidine isethionate and amphotericin B deoxycholate, agents that are as effective but more toxic. For visceral leishmaniasis (kala azar), liposomal amphotericin B is the only drug currently approved by the FDA (1). It is as effective and less toxic than pentavalent antimony (1). The recommended dosing for immunocompetent and immunocompromised patients is given in Table 22.5. Relapses are common in HIV-infected patients (1). In many areas of the world (because of cost), pentavalent antimony remains the drug of choice for initial treatment of visceral leishmaniasis (1,10). In the United States and other English-speaking countries, sodium stibogluconate (Pentostam) is available (through the CDC); in French-speaking and Latin American countries, meglumine antimoniate (Glucantime) is available. Sodium stibogluconate contains about 100 mg/mL of pentavalent antimony. The dosage recommended for visceral leishmaniasis is stibogluconate 20 mg/kg/day intravenously or intramuscularly for 28 days. Clinical response occurs in 92% to 98%. This treatment regimen can be repeated in unresponsive patients. For kala azar, pentamidine isethionate (Pentam) 2 to 4 mg/kg/day for up to 15 days is an effective alternative but is potentially toxic (1). Other alternatives include amphotericin B 0.5 to 1.0 mg/kg/day up to 1 to 3 g, amphotericin B lipid complex, and combinations of these agents with allopurinol or interferon gamma (1,5,10). It is recommended that patients with visceral leishmaniasis be hospitalized for treatment until they are stable (1). Splenectomy is indicated only in the rare case where hypersplenism persists after clinical response has occurred (1,2).

Pearson et al. (1) suggest that a decision whether or not to treat cutaneous leishmaniasis depends on the location and extent of lesion(s) and the species involved. For patients with lesions healing or located at a “cosmetically insignificant site” in areas of the world without mucosal disease, cutaneous leishmaniasis can be followed without therapy or treated topically (1). Large or disfiguring lesions should be treated. For treatment of cutaneous leishmaniasis, the drug of choice is sodium stibogluconate (Pentostam) 20 mg/kg/day intravenously or intramuscularly (maximum 800 mg/day) for 20 days (1,10). The treatment can be continued or repeated until there is a response. The suggested alternative drug is amphotericin B 0.5 to 1.0 mg/kg every day or every other day, respectively, up to 1 to 3 g. A combination of pentavalent antimony and concurrent interferon gamma has been successful in treating diffuse cutaneous leishmaniasis, a form of the disease that responds poorly to antimony only (1). Cutaneous disease due to *L. major* can be treated with topical paromomycin 15% twice a day for 15 days (1,10).

Mucosal leishmaniasis is less response to pentavalent antimony. In patients unresponsive to or relapsing after antimony therapy, amphotericin B 0.5 to 1.0 mg/kg intravenously every day or every other day (total dose 1.5 to 2.0 g) should be given.

Pentamidine isethionate 2 to 4 mg/kg once or twice weekly is an alternative choice.

The use of these drugs in pregnancy is limited, and their effects are not clear. They should be used with caution, and only treatment of visceral leishmaniasis (kala azar) seems appropriate during pregnancy.

Trypanosomiasis

There are two forms of human trypanosomiasis. Chagas disease (American trypanosomiasis) is caused by *Trypanosoma cruzi* and African sleeping sickness (African trypanosomiasis) by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense.* These two diseases differ in their geographic distribution, mode of transmission, pathogenesis, and clinical course (1). In fact, these two diseases have little in common except the morphologic similarities of the organisms (1).

Chagas Disease (American Trypanosomiasis)

Chagas disease is caused by *T. cruzi* and occurs in Central and South America and Mexico, where millions of people are infected with this protozoan parasite (2). *Trypansoma cruzi* is transmitted by blood-sucking triatomine insects (kissing bugs) that live in the cracks and holes of primitive dwellings in urban shanty towns (1,3). It is estimated that 16 to 18 million people are infected with *T. cruzi* worldwide. Chagas disease causes approximately 50,000 deaths annually (4). In the past, Chagas disease was a rarity in the United States. However, large-scale immigration to the United States from Central America has changed the situation dramatically. Kirchhoff (5) has estimated that as many as 50,000 to 100,000 immigrants infected with *T. cruzi* currently reside in the United States (5). Immunosuppression of patients with *T. cruzi* infection can result in reactivation of acute infection; thus, transplant patients and HIV-infected patients are at risk for recrudescence of acute Chagas disease.

The triatomine insects become infected by sucking blood from animals or humans with circulating trypomastigotes (1). The parasites multiply in the insects' midgut as epimastigotes. In the hindgut, they transform into metacyclic forms of *T. cruzi* that are the infective form and then deposited in feces as the insect trypomastigote feeds. The trypanosomes penetrate through the bite wound or mucous membranes (2). *Trypansoma cruzi* is capable of penetrating into mammalian cells, where it develops into a mastigote *(Leishmania)* form. Here the organism multiplies and forms a pseudocyst that ruptures with release of protozoan organisms that enter the bloodstream or invade adjacent cells (1). The cycle is completed when triatomine insects ingest human blood containing the parasites. Other modes for transmission of *T. cruzi* include blood transfusion in endemic areas, congenital infection, and laboratory accidents (1).

Programs in endemic countries have been implemented recently for vector and blood bank control. In particular, a major international control program involving Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay has led to decreased prevalence rates among the young and a prediction that if current trends continue, transmission will be virtually eliminated by year 2003 (6,7).

Clinical Presentation

The clinical course of *T. cruzi* presents as two distinct entities (1). Acute infection results at the initial encounter of the host and the organism. Chronic Chagas disease involves late sequelae of the infection.

Acute Chagas disease usually occurs in children. Although acute Chagas disease usually is mild, the disease can be very severe in immunocompromised patients. Only 1% of inhabitants of endemic areas who become infected develop clinically apparent acute disease. The most common site for the bite is the face. Urticaria often develops at the bite site, followed by an inflammatory nodule, the chagoma (1,3,4). The bite often is associated with Romaña sign (the classic sign of acute Chagas disease), which is unilateral nonpurulent edema of the palpebral folds and an ipsilateral regional lymphadenopathy (1,3,4). After 2 to 3 weeks, parasitemia occurs with widespread dissemination, fever, lymphadenopathy, malaise, and peripheral edema (1,3,4). *Trypanosoma cruzi* invades cells, resulting in the typical involvement of the heart, liver, gastrointestinal tract, and central nervous system (CNS). The cardiac disease that occurs in a small percentage is characterized by tachycardia, arrhythmia, hypotension, cardiomegaly, and congestive heart failure (1,4). *Trypanosoma cruzi* may invade the CNS and rarely causes meningoencephalitis. The mortality rate in the acute phase of Chagas disease is 10% to 20%, with most deaths secondary to cardiac disease or encephalitis. Acute Chagas disease generally resolves spontaneously over a 4- to 8-week period.

Chronic Chagas disease generally occurs in patients with no history of acute disease. It has a slow and insidious onset, occurring years and decades after the acute infection (1). Approximately 10% to 30% of individuals who harbor *T. cruzi* for years to decades develop symptoms of chronic Chagas disease. Cardiac involvement occurs in 20% to 40% of patients with chronic disease and presents as progressive cardiac enlargement in association with congestive heart failure and electrocardiographic evidence of arrhythmias. Emboli to the brain or other areas is a frequent complication (1). Involvement of chronic gastrointestinal disease is characterized by progressive development of megaesophagus or megacolon. Mortality rates of nearly 20% have been reported in association with chronic Chagas disease; approximately half the deaths are due to congestive heart failure secondary to cardiomyopathy (1,4). Immunosuppression of persons harboring *T. cruzi* chronically may lead to reactivation of infection, often with greater severity than is associated with acute infection in immunocompromised individuals (1).

Diagnosis

Diagnosis in the acute stage of Chagas disease can be made by demonstrating the protozoan *T. cruzi* on thin or thick smears of the blood or buffy coat. When examination of blood preparations or specimens from lymph node and bone marrow aspirates fails to detect *T. cruzi* in immunocompromised patients, attempts to culture blood or other specimens should be undertaken (1). Xenodiagnosis, which is performed by allowing laboratory-bred triatomids to feed on the patient and examining the fecal contents of the bugs for trypanosomes in 30 to 60 days, is available in endemic areas. Serologic tests for IgM antibody are available but are not well standardized. Chronic Chagas disease is suggested by the characteristic clinical picture and confirmed by serologic tests and/or by biopsy demonstration of *T. cruzi* in tissue. Indirect immunofluorescence, complement fixation, indirect hemagglutination, and ELISA tests are available to detect anti-*T. cruzi* IgG antibody. These serologic

tests are associated with false-positive results. Because of this lack of specificity, it has been suggested that specimens be tested with two or three serologic tests before the results are accepted as positive (1). In the United States, several kits for detecting antibodies to *T. cruzi* have been approved by the FDA: Chagas EIA (Abbott Laboratories, Abbott Park, IL, USA); Chagas IgG ELISA (Gull Laboratories, Salt Lake City, UT, USA); and Chagas' kit EIA (Hemagen Diagnostics, Waltham, MA, USA). In the future, serologic tests using antigens produced by recombinant DNA technology and/or PCR-based assays for detecting *T. cruzi* will become available and provide greater sensitivity and specificity.

Effects In Pregnancy

Congenital Chagas infection may cause spontaneous abortion, preterm birth, IUGR, and stillbirth (3). In South America, 1% to 10% of spontaneous abortions are attributed to Chagas disease (3,8). Infection of the placenta usually can be demonstrated in these cases (3). *Trypanosoma cruzi* reaches the placenta hematogenously and traverses the villi to the trophoblasts (3). After differentiating into the amastigote form, the organism remains in Hofbauer cells until it is released into the fetal circulation (3). Bittencourt (9) reported that 226 (8%) of 2,651 pregnant women had IgG antibody against *T. cruzi* and 28% of the seropositive pregnant women had parasitemia. Despite the high rate of parasitemia, the risk of transmission to the fetus is low (3,9).

Congenital infection with Chagas disease is reported to occur in 1% to 4% of deliveries in women with serologic evidence of Chagas disease (3,8,10). The congenitally infected neonate tends to be preterm and/or small for gestational age. Bittencourt (10) noted that approximately 36% of congenitally infected infants died before age 4 months. In addition, *T. cruzi* may be found in breast milk (11). Freilij and Alcheh (12) reported diagnostic and clinical findings in 71 children with congenital Chagas disease in Buenos Aires, Argentina. In infants younger than 6 months of age, the disease was diagnosed by detection of *T. cruzi* in the blood using the microhematocrit test. This test is a microscopic visualization of parasites at 400× magnification of a sample from the buffy coat of heparinized blood. Forty-six (64.8%) of the children with documented congenital Chagas disease had no clinical signs of infection (12). The most frequent clinical manifestation was hepatomegaly (18.3%) (12).

Cecilia et al. (13) noted that transplacental transmission of *T. cruzi* could occur in the United States. This word of caution was based on their data assessing the seroprevalence of antibodies to *T. cruzi* among pregnant Hispanic women in Houston. Their data demonstrated a confirmed seroprevalence of 0.3% (95% confidence interval, 0%–1%) (13). Edgcomb and Johnson (8) reported that cardiac involvement associated with acute Chagas disease often is more severe in pregnant and puerperal women than in nonpregnant women.

Treatment

The drug of choice for treatment of acute Chagas disease is nifurtimox (Lampit) in a daily regimen of 8 to 10 mg/kg given in four doses for 120 days (14). This drug is available from the CDC Service (770-639-3670 weekdays and 770-639-2888 off hours). In pregnant women with evidence of cardiac or CNS disease, treatment should be started promptly. Adverse side effects occur in many patients treated with

nifurtimox (1). Gastrointestinal side effects include abdominal pain, nausea, vomiting, anorexia, and weight loss. Neurologic symptoms include restlessness, insomnia, twitching, paresthesias, and seizures. The suggested alternative drug is benznidazole (Rochagan) 5 to 7 mg/kg/day for 30 to 90 days. Side effects include peripheral neuropathy, rash, and granulocytopenia. In Latin America, many experts consider benznidazole the drug of choice for treating Chagas disease (1). These agents reduce the duration and severity of acute and congenital Chagas disease; however, the parasite is eradicated from only 70% of treated patients. In the past, it was debated whether effective treatment was available for chronic Chagas disease and whether chronic disease should be treated with nifurtimox or benznidazole (1). According to Kirchhoff (1), an international or panel of experts has recommended that all patients infected with *T. cruzi* be treated with one of these agents regardless of their clinical status or the time since acute infection.

African Sleeping Sickness (African Trypanosomiasis)

African trypanosomiasis is caused by *Trypanosoma brucei gambiense* (West African disease) and *Trypanosoma brucei rhodesiense* (East African disease). Infection is transmitted to humans by the bite of the tsetse fly (1,15). An estimated 50 million persons are at risk for acquiring African trypanosomiasis, and tens of thousands of new cases occur each year (1). These trypanosomes remain extracellular and multiply in the bloodstream, where they are able to evade host immune destruction because they undergo antigenic variation (1,5,16).

Clinical Presentation

West African trypanosomiasis initially presents as a local lesion, the trypanoma, at the bite site, which ulcerates and resolves spontaneously over several weeks (1). Characteristically, lymphadenopathy occurs in the initial hematolymphatic stage, which lasts 6 months to 5 years and progresses insidiously to the later meningoencephalitic stage. In this stage, the patient develops increasing indifference and somnolence. The disease usually is fatal.

East African trypanosomiasis is a much more acute disease and is associated with more severe symptoms. The disease usually begins within a few days of the bite and presents with high fever, malaise, and headache. No lymphadenopathy occurs. Central nervous system involvement occurs early and is associated with rapid clinical deterioration (1). The disease is rapidly progressive, with death occurring in weeks to months.

Diagnosis

The diagnosis of African trypanosomiasis should be suspected when unexplained febrile illnesses occur in inhabitants of, or visitors to, areas endemic for the causative agents. If a chancre is present, fluid can be smeared on a slide and examined microscopically for motile trypanosomes. West African trypanosomiasis is characterized by the Winterbottom sign, which is lymph gland enlargement (usually posterior cervical) that is not tender and has the consistency of ripe plums. The optimum diagnostic test is lymph gland puncture to provide a wet smear for detection of trypanosomes (1). East African trypanosomiasis should be suspected when fever, headache, and weight loss develop in patients who recently returned from, or reside

in, Central Africa. Diagnosis is confirmed by demonstrating trypanosomes on a wet or stained thick smear of blood or after concentration procedures (1). Serologic tests are available, and high levels of serum IgM are considered pathognomonic whereas the presence of IgM in the cerebrospinal fluid is diagnostic (17). Examination of cerebrospinal fluid is mandatory in all patients suspected of having African trypanosomiasis.

Effect On Pregnancy

As noted by Lee (11), African trypanosomiasis usually produces such severe and progressive disease that pregnancy does not occur. However, the parasites *T. brucei rhodesiense* and *T. brucei gambiense* can be transmitted transplacentally (3). If the disease is acquired during pregnancy, abortion, preterm labor and delivery, and/or stillbirth may occur (3,18). East African trypanosomiasis has such a fulminant course that it usually kills the infected patient before gestation can be completed.

Treatment

Treatment of African trypanosomiasis traditionally was provided with suramin, pentamidines, and organic arsenicals. However, suramin and pentamidine do not penetrate the CNS well, and the arsenicals, which are more toxic, were reserved for treatment of disease with nervous system involvement. Eflornithine has demonstrated high efficacy in the treatment of West African trypanosomiasis (*T. brucei gambiense*) (1,14). It is effective in hematolymphatic and CNS disease. The dosage is 400 mg/kg/day intravenously in four divided doses for 14 days, followed by 300 mg/kg/day orally in four divided doses for 3 to 4 weeks. It has variable efficacy for East African trypanosomiasis (*T. brucei rhodesiense*). However, this drug is very expensive and is no longer produced. In the hemolymphatic stage of African trypanosomiasis, the drug of choice is suramin 100 to 200 mg (test dose) intravenously, followed by 1 g intravenously on days 1, 3, 7, 14, and 21 (14) or eflornithine. Suramin is available in the United States from the CDC. The alternative drug is pentamidine isethionate 4 mg/kg/day intramuscularly for 10 days. For late disease with CNS involvement, the drug of choice is arsenical melarsoprol (Arsobal) 2 to 3.6 mg/kg/day intravenously for 3 days; after 1 week, 3.6 mg/kg/day intravenously for three doses; repeated again after 10 to 21 days, or eflornithine. Melarsoprol is a highly toxic agent and must be given with great care. This drug is only available on request from the CDC. Recently, Burri et al. (19) assessed a new treatment schedule for melarsoprol for treatment of sleeping sickness due to *T. brucei gambiense.* The 10-day schedule of daily injections of 2.2 mg/kg on consecutive days was as effective and as well tolerated as the standard 26-day regimen. Alternatively, tryparsamide one injection of 30 mg/kg intravenously every 5 days to a total of 12 injections plus suramin one injection of 10 mg/kg intravenously every 5 days to a total of 12 injections can be used. The latter regimen can be repeated after 1 month. The usually fatal outcome of African trypanosomiasis supports the need for aggressive therapy with potentially toxic agents, even in pregnant women.

Malaria

Malaria, the most important of the protozoan infections, remains a major health problem in many tropical developing areas of the world and has a significant impact on maternal, fetal, and neonatal health (1,2,3,4 and 5). It is estimated that malaria

has a worldwide prevalence of more than 300 to 500 million and is associated with more than two to three million deaths per year (2,6,7). In the United States, malaria occurs as relapse in immigrants or in U.S. residents who traveled to an endemic area (2,8). It is a potentially life-threatening disease for nonimmune travelers to the tropics (2). The overwhelming majority of human malaria cases are caused by four species of the obligate intracellular protozoan parasite *Plasmodium*: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale.* Each of these species has its own morphologic characteristics and life cycle. Malaria transmission occurs worldwide. *Plasmodium falciparum* is associated with the greatest risk of death in nonimmune individuals because of its ability to invade red blood cells (RBCs) of all ages and its high rate of resistance to antimalarial agents (2). *Plasmodium falciparum* predominates in sub-Saharan Africa, Haiti, the Dominican Republic, and New Guinea. Both *P. falciparum* and *P. vivax* are prevalent in Southeast Asia, South America, and Oceania. Transmission of *P. vivax* also occurs in the Middle East, North Africa, Sudan, Ethiopia, and Somalia. *Plasmodium ovale* occurs primarily in sub-Saharan Africa. *Plasmodium malariae* is worldwide in distribution.

Approximately 1,000 cases of malaria in the United States are reported annually to the CDC (7). Of these cases, 50% occur in the non-U.S. citizens. However, the other 50% are in returning U.S. travelers. Thus, it is important that travelers to malaria-infested areas (e.g., sub-Saharan Africa) be informed about the risk of malaria and appropriate preventive measures, including chemoprophylaxis, be taken. Similarly, health care providers need to have a high index of suspicion for malaria so that timely diagnosis and appropriate lifesaving therapy are instituted.

Malaria is transmitted by the bite of infected female anopheline mosquitoes. Whereas asexual reproduction occurs in humans, sexual reproduction occurs in the mosquito. Following sexual reproduction, sporozoites, which are the infective form of *Plasmodium* sp, are stored in the salivary glands of the mosquito. After the sporozoites are inoculated by the mosquito bite into subcutaneous capillaries, they migrate via the bloodstream to the liver, where they invade hepatic cells (Fig. 22.3). In the liver, parasites exist as exoerythrocytic forms and multiply to form hepatic schizonts. Mature schizonts contain 7,500 to 40,000 merozoites, depending on the type of *Plasmodium* sp. Following rupture of the schizonts (after 1–2 weeks), the merozoites enter the bloodstream and invade erythrocytes. This invasion of the RBCs initiates the cycle of growth and multiplication known as schizogony and ultimately leads to destruction of the parasitized RBC (2,8,9 and 10).

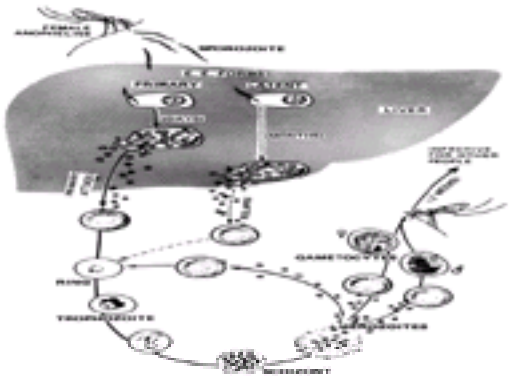


FIGURE 22.3. Life cycle of plasmodia in man. (From Wyler DJ, Miller LH. Plasmodium species. In: Mandel GL, Douglas RG, Bennett JE, eds. *Principles and practice of infectious diseases*. New York: John Wiley & Sons, 1979, with permission.)

With *P. falciparum* and *P. malariae,* all of the exoerythrocytic schizonts rupture at about the same time; thus, none persist in a latent form in the liver. For *P. vivax* and *P. ovale,* there are both primary exoerythrocytic forms that rupture to cause the initial episode of parasitemia and latent exoerythrocytic forms that remain in the liver for long periods before rupturing. Rupture of the latent hepatic schizonts is responsible for recurrent parasitemia and erythrocytic infection. Once *Plasmodium* organisms enter the erythrocytic stage, they never reinvade the liver.

After entering the RBCs, merozoites acquire a signet ring appearance, thus becoming ring forms. With an increase in cytoplasm as the asexual organism develops, the parasites are called trophozoites. Nuclear division then occurs, producing the schizont. Upon completion of asexual reproduction, 6 to 24 individual merozoites (depending on the species) are present in each schizont. Rupture of the schizont releases the merozoites into the bloodstream, where they rapidly attach to and invade new RBCs. This complete process requires 72 hours for *P. malariae* and 48 hours for *P. falciparum, P. vivax,* and *P. ovale.* Male and female gametocytes develop from a subpopulation of merozoites and then are ingested by female anopheline mosquitos during feeding (2,10). Sexual reproduction only occurs in the mosquito gut, and the fertilized zygotes invade the gut wall, where they develop into oocysts that contain thousands of sporozoites and migrate to the salivary glands. In addition to human-to-human transmission via a mosquito vector, malaria can be transmitted by transfusion of blood products and by shared syringes and needles among drug abusers.

Plasmodium falciparum infection is the most serious and life-threatening form of malaria. This organism parasitizes RBCs of any age and reaches very high concentrations in the bloodstream. A unique characteristic of *P. falciparum* is its ability to adhere to venular endothelium (8). Cytoadherence is due to knobs that appear on the surface of *P. falciparum*—parasitized RBCs containing mature parasite forms (2). As a result of this cytoadherence, mature asexual *P. falciparum* parasites are not present on peripheral blood smears but rather are sequestered in the peripheral and organ microcirculation (2). The sequestration protects *P. falciparum* parasites from being removed from the circulation by the spleen and from the oxidant effect of passing through the pulmonary capillary beds (2). As noted by Lee (10), it is the large numbers of parasitized RBC with altered rheologic and immunologic properties associated with *P. falciparum* infection that are responsible for the development of life-threatening complications, such as black water fever, pulmonary edema, and cerebral malaria, that occur almost exclusively with *P. falciparum* infection. Infection with *P. falciparum* has been complicated by the emergence of strains resistant not only to chloroquine but also to sulfonamides and pyrimethamine (2,5,11,12,13 and 14). Resistance to chloroquine is found among *P. falciparum* strains occurring in all countries with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America west of the Panama Canal, Mexico, and

parts of the Middle East. Resistance of *P. falciparum* to pyrimethamine-sulfadoxine (Fansidar) occurs in Southeast Asia, the Amazon basin area of South America, sub-Saharan Africa, Bangladesh, and Oceania (7,14). *Plasmodium falciparum* resistance also has been reported to mefloquine (Thailand and Cambodia) and quinine (Thailand) (14,15). Cases of chloroquine-resistant *P. vivax* infections have been reported in New Guinea, Indonesia, Myanmar, India, Irian Jaya, and the Solomon Islands (7, 14).

Clinical Presentation

The hallmark of malaria is the cyclic fevers that occur just before or at the time RBCs are lysed when schizonts rupture, releasing merozoites (2). This occurs every 48 hours with *P. vivax* and *P. ovale* infection (tertian malaria) and every 72 hours with *P. malariae* infection (quartan malaria). *Plasmodium falciparum* also has a 48-hour cycle, but continuous fevers with intermittent spikes usually are present (2). The classic finding of acute malarial infection is the malaria paroxysm, which is characterized by high fever, chills, and rigors (2). The paroxysm typically has three stages (2). Initially, patients present in the “cold stage,” in which they feel cold and have shaking chills. Within 15 minutes to 2 hours, the “hot stage” commences, with high temperatures (up to 40° C) but minimal diaphoresis. In addition, tachycardia, tachypnea, headache, backache, abdominal pain, nausea, vomiting, and delirium are present. The marked peripheral vasodilation produces a decrease in intravascular volume and results in orthostatic hypotension. Within 2 to 6 hours, the “sweating stage” begins, with diaphoresis, defervescence, and marked fatigue.

Plasmodium falciparum infection may progress rapidly to a severe multisystem disease that is potentially lethal (5). As reviewed by White (5), the clinical presentation of severe malaria is age dependent. Children more commonly develop hypoglycemia, convulsions, and severe anemia. Adults more commonly present with acute renal failure, jaundice, and pulmonary edema. Cerebral malaria, shock, and acidosis occur at any age (5). These serious complications of *P. falciparum* infection are the result of the more extensive sequestration of *P. falciparum* parasitized RBCs in the microvasculature and the more severe metabolic effects (e.g., hypoglycemia, lactic acidosis) associated with hyperparasitemia (2). Nonimmune persons are particularly at risk to develop life-threatening infections with *P. falciparum,* whereas individuals with partial immunity may tolerate high-level parasitemia without evidence of disease (2).

Sequestration does not occur with *P. vivax* or *P. ovale* infection (2). As a result, there are no multiorgan system microvascular complications. Moreover, all asexual forms of these parasites are present in the peripheral blood (2). The level of parasitemia generally is low. In *P. vivax* infection, the spleen is prone to rupture, and care must be taken during examination of the patient. *Plasmodium malariae*-parasitized RBCs also are not sequestered in the microvasculature. Thus, the level of parasitemia is low and symptoms are mild (2). Low-grade infection with *P. malariae* may persist for 2 to 30 years (2). An immune complex glomerulonephritis (parasite antigen plus host IgG) may occur (2). Malarial patients also demonstrate a normochromic normocytic hemolytic anemia, leukopenia, monocytosis, and thrombocytopenia.

In endemic areas, initial malaria infection occurs during childhood. Repeated clinical infections tend to be reduced in severity as a result of acquired cellular and humoral immunity (6). Nonimmune visitors to malaria endemic areas will have more severe

clinical disease than the immune local residents. Similarly, in pregnancy, the immune woman acquiring malarial infection suffers less severe infection than the nonimmune woman. For this reason, unless absolutely necessary, nonimmune pregnant women should not travel to malaria endemic areas, especially *P. falciparum* endemic areas.

Diagnosis

Diagnosis of malaria requires demonstrating *Plasmodium* parasites in stained peripheral blood smears obtained from patients with the characteristic malaria paroxysm. The thick smear is useful to detect the presence of parasites, and then a thin smear can be used to make a species diagnosis. Smears are stained with Wright-Giemsa or preferably 3% Giemsa solution. The malaria parasites are always intracellular with blue cytoplasm and a red chromatin dot. Examination of the peripheral smear for the presence of multiple infected RBCs, late-stage asexual parasites (trophozoites and schizonts), and enlarged parasitized RBCs allows differentiation between infection with *P. falciparum* and *P. vivax* or *P. ovale* (2). Multiple infected RBCs are common with *P. falciparum* and rare with *P. vivax* or *P. ovale*. On the other hand, mature parasites and enlarged RBCs with later parasite stage are common in *P. vivax* or *P. ovale* infection but absent with *P. falciparum*. Quantitation of parasitemia is used to evaluate response to therapy. Smears should be examined every 12 hours because they initially may be negative.

Effect On Pregnancy

Bruce-Chwatt (16) and Gilles et al. (17) demonstrated that malaria is more frequent during pregnant women than in nonpregnant patients. In addition, Bruce-Chwatt (16) and Reinhardt (18) suggested that there is an increased susceptibility to malaria during the first pregnancy. Several clinical investigations documented that malarial attacks, especially with *P. falciparum* during pregnancy, are likely to be more severe than in nonpregnant women (18,19 and 20). In particular, *P. falciparum*-infected pregnancy women are at risk for hypoglycemia. In malaria endemic regions, acquired immunity to malaria is commonly lost or impaired during pregnancy (2). It appears that nonimmune pregnant women are more susceptible to severe malaria, and fetal loss (abortions and stillbirth) is associated with severe disease (8).

As noted by Lee (10), a gradient of clinical illness with malaria in pregnancy exists. Pregnant women not immune to drug-resistant *P. falciparum* develop the most severe illness. Moderately severe malaria with fever and anemia occurs in nonimmune women with species of *Plasmodium* susceptible to chloroquine. These patients are also at risk for congenital malaria and IUGR. Reactivated latent disease occurring in an immune pregnant woman is associated with mild illness and placental infection but not fetal infection. The other extreme—acquisition of malaria in the nonimmune mother—can result in life-threatening disease and a high risk for fetal loss.

Malaria infection in pregnant women is associated with low birthweight, IUGR, preterm birth, spontaneous abortion, and stillbirth (16,17,18,19,20,21,22,23,24, 25,26,27,28,29,30,31,32,33,34,35,36 and 37). In addition, maternal anemia secondary to hemolysis is a major consequence of malaria. Reinhardt (1) demonstrated that mothers with low birthweight infants (<2,500 g), preterm deliveries (<37 weeks), and small-for-gestational age infants had significantly higher antibody titers against *Plasmodium* than did control patients. This association between maternal malaria

and low birthweight offspring was confirmed by several reports (16,21,22,23,24 and 25,33,34,35,36 and 37). Low birthweight occurs more frequently in pregnancies in which the placenta has been infected with the parasites (10,16,25). Cannon (25) postulated that placental infestation with parasites and the associated infiltration of lymphocytes and macrophages interfere with placental circulation and result in diminished transplacental transport of oxygen and nutrients to the fetus. Jelliffe (21) proposed that the intensity of placental infestation is proportional to the severity of the effect on the fetus. In a study from Malawi, Sullivan et al. (37) noted that the timing and severity of malaria infection influence the occurrence of IUGR and preterm delivery. Cord blood parasitemia and postdelivery maternal parasitemia were associated with preterm delivery, whereas parasitemia and/or clinically diagnosed malaria in the antenatal period were associated with IUGR. Thus, they suggested that IUGR results from placental insufficiency during the antenatal period (37). Preterm delivery, on the other hand, appears to be caused by mechanisms similar to those seen with other infectious diseases.

Fetal mortality rates (predominantly spontaneous first trimester abortions) have ranged from 14% to 60% (12,25,26,27,28,29,30,31 and 32). In addition, malarial infection during pregnancy increases the risk for stillbirth, prematurity, and neonatal mortality (10,24,29). Reinhardt (1) suggested several mechanisms by which congenital malaria occurs: (a) transplacental passage of parasites; (b) inoculation of parasites from maternal into fetal blood via skin abrasions at time of delivery; and (c) passage of parasites into amniotic fluid. Initial studies demonstrated that despite high rates of placental infection (16%–37%) congenital malaria (cord blood or neonatal parasitemia) was rare (<1%) (16,21,25,38). More recent studies suggest that although cord parasitemia may be more common than initially reported, the presence of parasites does not document that the infant will become infected (3). In the neonate, congenital malaria presents with fever, hepatosplenomegaly, jaundice, and anemia 48 to 72 hours after delivery. Finally, malaria may interfere with immune defense mechanisms and subject mother and fetus to an increased risk of bacterial or viral infection (1).

Treatment

There are four major groups of antimalarial agents currently available (Table 22.5) (2). These include (i) quinolone derivatives, including chloroquine, quinine, mefloquine, and halofantrine; (ii) antifolates, such as pyrimethamine and sulfonamides; (iii) artemisinin derivatives (e.g., quighaosu); and (iv) ribosomal inhibitors (e.g., tetracycline and clindamycin). As reviewed by White (5), the treatment of malaria depends on (i) severity of infection; (ii) patient age; (iii) degree of background immunity; (i) pattern of susceptibility to antimalarial agents; and (v) cost and availability of antimalarial agents. As a result, treatment recommendations vary according to the geographic region where infection occurred. Increasing resistance to chloroquine and antifolate is a major problem for the treatment and control of malaria (2). Krogstad (2) noted that the increasing prevalence of antimalarial resistance is the single most important factor in the current worldwide resurgence of malaria.

Chloroquine-Sensitive Plasmodium Species

Chloroquine is active against the asexual stages of susceptible strains of *P. falciparum, P. vivax, P. ovale,* and *P. malariae.* It is rapidly absorbed orally and can

be safely used in pregnant women. Oral chloroquine phosphate is the drug of choice for all malarial infections not due to chloroquine-resistant *P. falciparum* (2,14). Known chloroquine-sensitive *P. falciparum* organisms are found in North Africa, Central America north of the Panama canal, Haiti, and the Middle East. The dosage is 1 g orally, followed by 500 mg in 6 hours and then 500 mg/day for 2 days. Even with involvement of the CNS, there is no advantage to alternative antimalarials over chloroquine for treatment of chloroquine-susceptible malarial organisms (2). Pruritus is a common side effect of chloroquine. Parenteral therapy, if required, consists of quinidine gluconate 10 mg/kg loading dose intravenously over 1 to 2 hours, followed by a continuous infusion of 0.02 mg/kg/min until oral therapy can be instituted. Patients receiving intravenous quinidine require cardiac monitoring and close monitoring of fluid status. Artemether is an alternative parenteral antimalarial. Parenteral therapy generally is necessary only with severe *P. falciparum* disease. Chloroquine alone treats only the erythrocytic stage of malaria. Thus, patients with *P. vivax* and *P. ovale* require additional treatment for the latent exoerythrocytic hepatic schizonts. These forms are eradicated by primaquine phosphate 26.3 mg (15 mg base) orally every day for 14 days or 79 mg (45 mg base) per week for 8 weeks. Patients receiving primaquine should first be screened for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Primaquine should not be used during pregnancy because the drug may cross the placenta and cause hemolytic anemia *in utero* to a G-6-PD–deficient fetus. Whenever cure with primaquine is indicated, chloroquine should be given once a week until delivery, when primaquine may be started.

Chloroquine-Resistant *Plasmodium* Species

Quinine is effective against all *Plasmodium* sp. However, it generally is used only for treatment of chloroquine-resistant *P. falciparum* infection. Mild-to-moderate malaria due to chloroquine-resistant *P. falciparum* is treated with a combination of quinine sulfate 650 mg orally three times a day for 3 days, plus doxycycline 100 mg orally twice a day for 7 days. *Plasmodium falciparum* infection acquired in Southeast Asia is more resistant and requires 7 days of quinine therapy. Alternative regimens for *P. falciparum*-resistant malaria include (i) quinine sulfate plus pyrimethamine-sulfadoxine (Fansidar) or clindamycin; (ii) mefloquine hydrochloride (Lariam); (iii) halofantrine (Halfan); (iv) atovaquone plus proguanil or doxycycline; or (v) artesunate plus mefloquine. Halofantrine is contraindicated in pregnant or lactating women. Most *P. falciparum* organisms that are resistant to mefloquine also are resistant to halofantrine (2); therefore, halofantrine should not be used in patients who failed prophylaxis with mefloquine. For chloroquine-resistant *P. vivax,* the drug of choice is quinine sulfate plus doxycycline or pyrimethamine-sulfadoxine. Quinidine is the drug of choice for parenteral therapy of all *Plasmodium* sp. It is twofold to threefold more active than quinine, and serum levels can be measured. Parenteral quinine is no longer available in the United States (2).

Malaria in Pregnancy

Chloroquine, pyrimethamine-sulfadoxine, quinine, quinidine, and clindamycin are considered safe at therapeutic doses in all trimesters of pregnancy (5). Although mefloquine was believed safe to use in the second and third trimesters of pregnancy (5,39), a report from Thailand demonstrated that mefloquine treatment during pregnancy was associated with an increased risk of stillbirth (41). These authors reported that mefloquine was not associated with abortion, low birthweight,

neurologic retardation, or congenital malformation (40). Use of artemisinin derivatives in pregnancy has not been well studied. It is believed they may be used for mefloquine-resistant *P. falciparum* malaria in the second and third trimester (5,41). In the first trimester, quinine is the preferred choice (41).

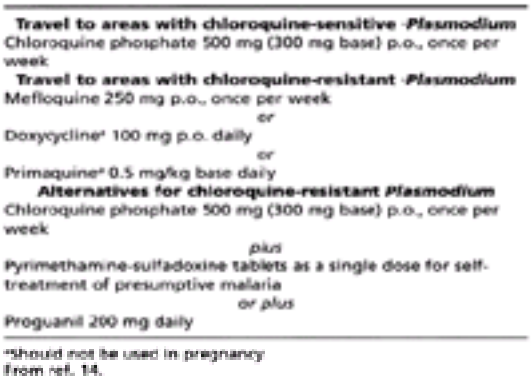
Experimental data demonstrating the teratogenic effect of pyrimethamine in laboratory animals have raised concern over its use in pregnancy. However, published data do not substantiate that pyrimethamine is a teratogen in humans (42). Concomitant folinic acid should be used with pyrimethamine-containing combinations. Tetracycline is best avoided in pregnancy. Thus, all the antimalarial drugs except primaquine, tetracycline, and halofantrine can be used in pregnant and lactating women (5).

For nonchloroquine-resistant malaria of all types in pregnant and lactating women, chloroquine is the treatment of choice given at a dose of 1 g, then 500 mg at 6, 24, and 48 hours. For *P. vivax* and *P. ovale* disease, this dosage is continued on a once-a-week basis until after delivery, when it is safe to give primaquine 15 mg base daily for 14 days to eradicate liver forms of these parasites (2,5). Quinine plus pyrimethamine-sulfadoxine (Fansidar) regimen or a quinine plus clindamycin (900 mg orally, every 8 hours for 3 days) should be used for the treatment of pregnant women with chloroquine-resistant *P. falciparum* infection. Severe infection in pregnant women with *P. falciparum* should be treated with quinidine gluconate or dihydrochloride given as a slow intravenous drip, as described earlier.

In nonimmune pregnant women, clinical episodes of malaria should be treated promptly. This is true even though all the antimalarial agents have potentially adverse effects on the fetus (10). Chloroquine may produce retinal and cochleovestibular damage; quinine is ototoxic; primaquine may cause hemolysis in G-6-PD–deficient patients, as well as methemoglobinemia; and pyrimethamine may be teratogenic. Essentially, the treatment regimens for malaria in pregnant women are similar to the regimens for nonpregnant patients. Exceptions include primaquine, tetracycline, and halofantrine, which should not be given in pregnancy. Malaria with *P. falciparum* should be viewed as a medical emergency in pregnancy, and patients from areas with chloroquine-resistant *P. falciparum* should be reated with multiple drug regimens including quinine and pyrimethamine/sulfonamides.

Prevention of Malaria

Chemoprophylaxis should be provided for travelers to endemic malarial areas (Table 22.7) (14). Chemoprophylactic agents should be started 2 weeks before departure in order to provide an opportunity to change drugs if significant side effects occur. The chemoprophylactic agents should be continued for 4 weeks after leaving the endemic area to provide coverage against infection acquired just before departure.



Travel to areas with chloroquine-sensitive *Plasmodium*
Chloroquine phosphate 500 mg (300 mg base) p.o., once per week
Travel to areas with chloroquine-resistant *Plasmodium*
Mefloquine 250 mg p.o., once per week
or
Doxycycline[a] 100 mg p.o. daily
or
Primaquine[a] 0.5 mg/kg base daily
Alternatives for chloroquine-resistant *Plasmodium*
Chloroquine phosphate 500 mg (300 mg base) p.o., once per week
plus
Pyrimethamine-sulfadoxine tablets as a single dose for self-treatment of presumptive malaria
or plus
Proguanil 200 mg daily

[a]Should not be used in pregnancy
From ref. 14.

TABLE 22.7. CHEMOTHERAPEUTIC AGENTS USED FOR PREVENTION OF MALARIA

The usual prophylactic regimen for travel to areas where chloroquine-resistant *P. falciparum* has not been reported or where only low-level resistance has been reported is chloroquine phosphate 500 mg (300 mg base) orally once per week beginning 1 to 2 weeks before departure and continuing for 4 weeks after leaving the endemic area. Common side effects include headache, dizziness, and blurred vision. These symptoms are transient and can be controlled by taking half the dose twice a week (2). The use of mosquito netting and insect repellant is crucial to prevention programs.

Travelers to areas where chloroquine-resistant *P. falciparum* is endemic (Southeast Asia, Amazon region, South America, and sub-Saharan Africa) should be given a dose of mefloquine (Lariam) 250 mg orally, once per week. Doxycycline 100 mg alone, taken daily, is an alternative regimen for short-term travel to chloroquine-resistant *P. falciparum* endemic areas (14,43). Doxycycline prophylaxis can begin 1 to 2 days before travel and continued for 4 weeks after departure from the malarious area. A second alternative is primaquine (0.5 m/kg base daily) (44,45). An additional chemoprophylactic agent in chloroquine-resistant areas is a combination of chloroquine phosphate 500 mg orally once a week plus pyrimethamine-sulfadoxine as a single dose (three tablets) for presumptive treatment of febrile illness or plus proguanil 200 mg/day (not available in United States) To prevent relapses due to liver forms of *P. vivax* or *P. ovale,* primaquine is recommended. However, prophylaxis with primaquine generally is indicated only for persons who had prolonged exposure in malaria endemic areas. It is administered after the traveler leaves an endemic area and usually in conjunction with chloroquine during the last 2 weeks of the 4-week period of prophylaxis after exposure in an endemic area has ended.

As discussed previously, malaria infection can be more severe in pregnant than nonpregnant women, and chloroquine is safe to use in pregnancy. Thus, pregnancy is not a contraindication for chemoprophylaxis with chloroquine phosphate 500 mg (300 mg base) weekly in areas without chloroquine-resistant malaria (9). However, for areas with chloroquine-resistant malaria, the alternative drugs mefloquine, doxycycline, and primaquine should not be used in pregnancy (9,14). In these areas, the combinations of chloroquine phosphate plus pyrimethamine-sulfadoxine for

presumptive treatment or plus proguanil appear to be safe in pregnancy (14,46). Some have recommended that women who are pregnant or likely to become pregnant should avoid travel to areas with chloroquine-resistant *P. falciparum* (9). Current information on malaria in specific countries and on antimalarial chemoprophylaxis can be obtained from the Malaria Branch, Division of Parasitic Diseases, CDC (770-488-4046). In addition, the CDC information service has added facsimile capability to malaria hot lines (770-332-4555) that provide faxed information on the risk for malaria, prevention measures, and effects on pregnancy (9).

Toxoplasmosis

Toxoplasmosis is the infection caused by the protozoan parasite *T. gondii.* This disease is discussed in Chapter 16.

Trichomoniasis

Trichomoniasis is a vaginal infection caused by the anaerobic protozoan parasite *Trichomonas vaginalis*. This entity is discussed in Chapter 12.

Pneumocystis

Pneumocystis carinii is an opportunistic protozoan parasite that causes *P. carinii* pneumonia in immunocompromised patients. This is particularly true in HIV-infected individuals. This entity is discussed more fully in Chapter 9.

HELMINTHS

Helminths, or worms capable of parasitizing humans, are ubiquitous organisms occurring with a wide geographic distribution (especially prevalent in tropical regions). They are unique organisms among the infectious agents (1). They may be the most prevalent of human infectious agents. *Ascaris, Trichuris,* and the hookworms account for one billion infections each, and schistosomes and filariae account for 250 million infections each (2). Warren (3) estimated that over 54 million helmintic infections are present in the United States, the majority due to enterobiasis.

Three major groups of parasitic helminths infect man: Nematoda (roundworms) and two groups of Platyhelminthes (flatworms). The flatworms include the trematodes (flukes) and cestodes (tapeworms) (Table 22.8).

Organism	Common Name
Nematodes	
Ancylostoma duodenale	Hookworm
Ascaris lumbricoides	Ascaris (giant roundworm)
Enterobius vermicularis	Pinworm
Onchocerca volvulus	River blindness
Strongyloides stercoralis	Strongyloidiasis
Trichinella spiralis	Trichinosis
Trichuris trichiura	Whipworm
Wuchereria bancrofti	Filariasis
Trematodes	
Clonorchis sinensis	Liver fluke
Fasciola buski	Liver fluke
Paragonimus westermani	Lung fluke
Schistosoma haematobium	Blood fluke
Schistosoma japonicum	Blood fluke
Schistosoma mansoni	Blood fluke
Cestodes	
Diphyllobothrium latum	Fish tapeworm
Taenia saginata	Beef tapeworm
Taenia solium	Pork tapeworm
Echinococcus granulosis	Hydatid cyst

TABLE 22.8. MAJOR HELMINTIC INFECTIONS OF HUMANS

There are several unique characteristics of the helminths as infectious agents (1,2). They are large enough to be seen by the naked eye (macroparasites). The life cycle of worms is complex and often involves at least two hosts (1). As reviewed by Mahmoud (1), helmintic infections in humans are initiated by ingestion of eggs or penetration of intact skin by infective larvae (1). Once in the human host, worms undergo maturation and differentiation into the adult sexually mature form. The mature worms produce eggs or larvae that continue the life cycle by transmitting infection outside the human host (1). Once organisms are passed into the environment, they invade intermediate hosts (e.g., snails, pigs) where asexual multiplication and maturation into the infective stage (for humans) occurs. For some worms, a simpler life cycle exists: transmission stages of the worms undergo changes upon leaving the human host that allow direct infection of humans without the need for an intermediate host (1). Reproduction requires completion of the life cycle outside the human host. Thus, with but rare exception, helminths do not multiply in the human host, and the infestation size is determined by the number of worms initially acquired or acquired through repeated exposure to infectious larvae or eggs. Disease and morbidity associated with helmintic infections are basically a function of the quantity of worms in the body.

As noted by Lee (4), complex mechanisms of disease production in humans exist for helmintic infection; they may be caused by the adult worm or its ova or larvae. Schistosomes produce disease secondary to inflammation produced by eggs or cercaria. Filariae obstruct lymphatic channels, and other helminths produce disease during migration of the adult worms or larvae. The intestinal helminths may produce disease by competing with the host for nutrition or by causing anemia secondary to blood loss. As noted by Liu and Weller (5), disease expression is determined primarily by the acquired worm burden and exposure history. Thus, the clinical presentation is different among lifelong residents of endemic areas as compared to travelers or immigrants in nonendemic areas. For the majority of helmintic infections, transient exposure results in lower worm burden and less severe disease.

Helminths use a variety of strategies to evade the host defense mechanisms (1). Examples include (i) encapsulation within a host fibrous reaction (hydatid cyst); (ii) intraluminal presence (*Ascaris*); (iii) immunosuppression (filariasis); and (iv) acquisition of host antigens (schistosomes). Helmintic infections are characterized by the presence of eosinophilia (1). Eosinophilia is associated with tissue migratory stages of these infections and is not observed in infections with worms located in the gut (i.e., tapeworm) (1).

Nematoda (Roundworms)

Ascariasis

Ascariasis is the most common helmintic infection of man, with an estimated one billion cases. *Ascaris lumbricoides,* the causative agent, is most abundant in tropical

areas, especially those with soil contaminated by human feces. It is estimated that nearly four million cases exist in the United States, particularly in the Southeast (3,6). Transmission of ascaris is usually hand to mouth. Ascariasis is asymptomatic in the overwhelming majority of cases but occasionally may produce serious and fatal disease. Infection with *Ascaris lumbricoides* can occur in all age groups, but is most common in preschool and young school-aged children (2).

Adult forms of *A. lumbricoides* inhabit the lumen of the small intestine. Female worms daily lay 200,000 ova, which pass with feces. Following passage, fully developed infective embryos are formed within the eggs in 5 to 10 days (7). Following ingestion of infective embryonated eggs, the eggs hatch in the small intestine, where the larvae penetrate through the mucosal lining to enter the portal vein system or intestinal lymphatics (7). They then migrate via the venous system to the lungs, where the larvae penetrate into the alveolus and migrate up the bronchi and trachea and are swallowed. Maturation into the adult worm occurs in the small intestine with a life span of 10 to 24 months.

Only a few worms are present in the vast majority of *Ascaris* infections; in these instances, infection is not clinically apparent (7,8). On occasion, a single worm may produce clinical disease by migrating to an important anatomic location, such as the biliary duct or appendix. Nutritional disorders (impaired digestion or absorption of protein) occurs, especially in children (2). When heavy infestation is present, the chance for adult worms to migrate is greater, and thus the risk for clinically apparent disease is increased (7). Intestinal obstruction is a rare serious complication caused by a bolus of worms. If many eggs are ingested, larval migration produces symptomatic pulmonary disease with nocturnal cough and eosinophilia. Fever, rales, persistent cough, and transient radiographic infiltrates may be present as well. Adult *Ascaris* has been reported to invade the female genital tract to cause tuboovarian abscess (9). Similarly, Sterling and Guay (10) reported invasion of the female genital tract by *A. lumbricoides.* Congenital *Ascaris* infection is rare, although Chu and coworkers (11) described an infant who delivered in association with 12 adult *Ascaris* worms.

The diagnosis of ascariasis is made by demonstrating *Ascaris* eggs in the stool, recovering an adult worm, or seeing larvae on sputum or gastric aspirates. Each female worm produces 200,000 ova daily (1); thus, direct smear examination of stool is sufficient to make the diagnosis (1).

In nonpregnant patients with ascaris, mebendazole (Vermox) is the treatment of choice at a dosage of 100 mg twice a day for 3 days or 500 mg once (Table 22.9) (1,12). This drug is poorly absorbed from the gastrointestinal tract and thus is free of toxicity. However, it is teratogenic in animals, and it has been recommended that mebendazole not be used in pregnancy (13). In Sri Lanka, routine administration of mebendazole to pregnant women after completion of the first trimester has been recommended since the 1980s (12). In a cross-sectional study of pregnant women, de Silva et al. (12) noted that mebendazole therapy during pregnancy was not associated with a significant increase in major congenital defects, even among women who took mebendazole during the first trimester. However, these authors cautioned that mebendazole is best avoided during the first trimester (12).

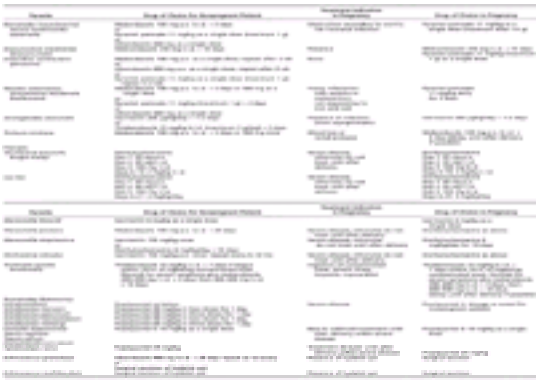


TABLE 22.9. RECOMMENDED THERAPY FOR COMMON HELMINTIC INFECTIONS

Alternative drugs for treatment of ascariasis include pyrantel pamoate 11mg/kg as a single dose (maximum 1 g) or albendazole 400 mg as a single dose (14). Both of these drugs have been approved by the FDA. When intestinal or biliary obstruction is present, piperazine citrate (Antepar) also should be administered (150 mg/kg initially, followed by six doses of 65 mg/kg at 12-hour intervals). It is administered as a syrup via a nasogastric tube (1). Piperazine narcotizes the worms and helps relieve intestinal or biliary tract obstruction (11).

During pregnancy, pyrantel pamoate (Antiminth) 11 mg/kg once (maximum dose 1 g) is the recommended therapy. Piperazine citrate is the alternative drug in pregnancy. Treatment in early pregnancy should be given to mothers with heavy worm infestation. The lightly infected mother should be treated immediately before or after delivery because of the risk of neonatal infection (4).

Enterobiasis

Enterobius vermicularis, the pinworm, is a highly prevalent worm widely distributed throughout the world, particularly in the temperate zone. Enterobiasis is the most common helmintic infection in the United States, with an estimated 42 million cases (7). It has a simple life cycle in which ingested infective eggs hatch into larvae in the duodenum and mature into adults within the gut lumen (7). The fertilized female pinworm contains over 10,000 eggs and at nighttime migrates to the perianal and perineal area, where the eggs are deposited. The eggs are infective within a few hours, and thus autoinoculation may occur. The eggs remain viable and infective for 7 to 10 days and are widely disseminated in the local environment. Thus, pinworm infestation occurs in multiple family members.

The vast majority of pinworm infections are asymptomatic (7). Clinical findings are generally limited to perianal and perineal pruritus. Frequently, the itching occurs at nighttime. Migrant pinworms have been noted to ascend the vagina, producing vaginitis (9) and occasionally pelvic inflammatory disease (15). Lee (4) suggested that pregnancy may exacerbate symptoms of vaginitis and/or pruritus vulvae. No

congenital infection has been described.

Diagnosis depends on demonstrating the presence of pinworms on adhesive cellophane tape applied to the perianal region first thing in the morning. Mebendazole (Vermox) as a single 100-mg dose (repeated after 2 weeks) is the drug of choice in nonpregnant patients but should not be used during pregnancy (Table 22.9). Albendazole as a single 400-mg oral dose, repeated in 2 weeks, or pyrantel pamoate (Antiminth), at a dosage of 11 mg/kg up to 1 g as a single dose repeated in 2 weeks, may be used. Pyrantel pamoate is the drug of choice for pregnant women.

Hookworm

Hookworm infection has a widespread geographic distribution in tropical and subtropical regions of the world (7). It is estimated that one fourth of the world's population is infected with hookworm (7). Hookworm is caused by infection of the small intestine with *Ancylostoma duodenale* (Old World hookworm) or *Necator americanus* (New World hookworm). The latter is fairly prevalent in southeastern United States (3).

Human infection occurs when hookworm larvae penetrate through the skin (7). At least 5 to 10 minutes of contact with contaminated soil is required for penetration to take place. The larvae enter the bloodstream and are carried to the lungs, where they emerge into alveoli, ascend up the bronchi and trachea, and then are swallowed. Larvae mature into adult worms in the small intestine, and the adult forms live attached to the mucosa of the small intestine. The female worm daily produces an average of 7,000 eggs, which are passed in the feces. Under suitable soil conditions, the eggs hatch into larvae that molt to become infective for humans.

The clinical presentation in hookworm infection depends on the stage of infection and the number of invading worms (7). In the initial stage, a pruritic vesiculopapular rash may be noted at the skin site where invasion by infective larvae occurred. Migration of larvae via the lung may result in cough, wheezing, fever, and eosinophilia. The major chronic manifestations of hookworm disease are related to the number of parasites present and include iron deficiency anemia and hypoalbuminemia due to blood loss caused by the hookworm. Langer and Hung (16) noted that previously asymptomatic hookworm infection may become clinically manifest in situations associated with increased iron needs, such as pregnancy and lactation. Diagnosis of hookworm disease depends on demonstration of eggs in direct fecal smears.

Hookworm infection in pregnancy without anemia or malnutrition does not require treatment. Replacement of iron, vitamins, and protein often suffices. However, if this nutritional support is not adequate, specific hookworm treatment is necessary. Mebendazole is the drug of choice in nonpregnant patients at a dosage of 100 mg twice a day for 3 days (Table 22.9). However, it is teratogenic in animals and is best not used in pregnancy (13). de Silva et al. (12) demonstrated that mebendazole is safe for use after the first trimester of pregnancy. In pregnant patients, pyrantel pamoate at a dosage of 11 mg/kg (maximum 1 g) daily for 3 days is the recommended drug for treatment of hookworm. In nonpregnant patients, albendazole 400 mg as a single dose or pyrantel pamoate are alternative agents for treatment of

hookworm.

Strongyloidiasis

Strongyloides stercoralis is capable of producing severe, potentially fatal infection because of its ability to cause overwhelming autoinfection, especially with alterations in the host immune system (7,17). Pregnancy and HIV infection are examples of such an occurrence. *Strongyloidiasis* is relatively uncommon compared to the other nematodes but is widely distributed in the tropics (7). It has been estimated to exist in from 0.4% to 4% of people in southern United States (3,7).

Stronglyoides stercoralis survives and reproduces in man or in suitable soil (5). It is the only common nematode parasite that can complete its life cycle in the human host (7,17). The parasites are acquired from infected soil, where the filariform larvae penetrate the skin. They then enter the bloodstream and migrate to the lungs. The larvae break into alveoli, ascend the trachea, and are swallowed. The adult form resides in the duodenum and upper jejunum, where the females deposit ova as they burrow into the intestinal mucosa. Because the adult female *S. stercoralis* dwell within bowel tissue, adult worms are not detectable in stool (5,17). In addition, the adult females reproduce by parthenogenesis and produce relatively few eggs (50 per day), which immediately release first-stage or rhabditiform larvae. As a result, the eggs of *S. stercoralis* also are not present in stool. The majority of rhabditiform larvae are evacuated in feces and develop into free-living adult worms, which in turn produce another generation of rhabditiform larvae that molt into filariform larvae, the infectious form of *S. stercoralis*. Penetration of the skin or mucous membranes by filariform larvae initiates *Strongyloides* infection.

Alternatively, rhabditiform larvae may develop directly into filariform larvae while they are still in the host intestine. These larvae penetrate the intestinal mucosa, establishing an “autoinfection” cycle. It is this ability of *S. stercoralis* to cause direct or autoinfection that results in serious infection. The process of autoinfection can accelerate, with a resultant rapid increase in the quantity of *S stercoralis* leading to the syndrome of hyperinfection strongyloidiasis. If not controlled, this can progress to disseminated strongyloidiasis with filariform larvae spreading to organs other than the gastrointestinal tract or lung.

Approximately one third of humans with *S. stercoralis* infestation are asymptomatic (5,7). In the remaining symptomatic patients, the symptoms of strongyloidiasis depend on the stage of infection (7). Skin invasion produces a pruritic papular erythematous rash. Migration of larvae through the lungs is associated with a Loeffler-like syndrome of chest symptoms, diffuse opacities on x-ray film, and eosinophilia in sputum and blood (5,7,17). Most commonly seen are the signs and symptoms associated with the intestinal phase of *Strongyloides* infection. Diarrhea, abdominal pain, and eosinophilia are characteristic findings. The large numbers of intestinal worms may produce malabsorption, protein-losing enteropathy, and iron deficiency anemia (5,7,17). The widespread use of immunosuppressive drugs in clinical medicine has led to an increased occurrence of hyperinfection and disseminated disease with *S. stercoralis* (5). More recently, hyperinfection strongyloidiasis has been described in patients with HIV infection (18). Hyperinfection usually presents with abdominal pain, anorexia, nausea, vomiting, or diarrhea. As the increasing number of worms disrupt the bowel mucosa, severe steatorrhea, malabsorption, protein-losing enteropathy, and paralytic ileus may develop. As large

numbers of filariform larvae perforate alveoli, cough, wheezing, and hemoptysis occur in association with diffuse alveolar and intestinal infiltrates on chest x-ray film. Uncontrolled hyperinfection progresses to disseminated disease in which filariform larvae penetrate organs not usually involved in the life cycle of *S. stercoralis.* These organs include the urinary tract, liver, and brain. In this stage, bacterial infection with enteric microorganisms such as *Escherichia coli* and *Klebsiella* dominates the clinical picture, with occurrence of septicemia, pneumonia, and meningitis. Mortality is high with disseminated strongyloidiasis and is due to a combination of parasite-induced damage, bacterial superinfection, underlying debilitation, and impaired host defenses (5,7,17).

Diagnosis depends on demonstrating *S. stercoralis* larvae in feces or aspirated duodenal fluid. Sampling of duodenal contents is best accomplished using the Enterotest (Hedeco, Palo Alto, CA, USA). Recently, a modified agar plate method of stool culture techniques was introduced that appears to be superior to other stool culture techniques for diagnosis of *S. stercoralis* (19). Serodiagnosis ELISA testing has demonstrated excellent sensitivity (85% to 90%) and specificity (90%). However, ELISA cannot quantitate the worm load and cannot distinguish between acute and past infection. Use of DNA probes appears to offer promise for diagnosis of *Strongyloides* (20).

Strongyloidiasis is the most difficult intestinal nematode infection to treat. Only total eradication of *S. stercoralis* can prevent the development of serious disease due to hyperinfection and disseminated strongyloidiasis. Unfortunately, this requires elimination of the autoinfective form, the filiform larvae of which are relatively resistant to available chemotherapeutic agents. According to *The Medical Letter,* ivermectin is the drug of choice for treatment of strongyloidiasis at a dosage of 200 µg/kg/day for 1 to 2 days (Table 22.9) (14). However, this drug currently is not approved by the FDA for treatment of disseminated strongyloidiasis. Thus, the alternative agent thiabendazole (Mintezol) may be preferred (14). Thiabendazole is an effective drug that is given at a dosage of 25 mg/kg twice a day (maximum 3 g/day) for 2 days (Table 22.9). In immunocompromised patients or those with disseminated disease, it may be necessary to repeat therapy or prolong therapy for 2 to 3 weeks (7). Because of the risk for hyperinfection associated with immunosuppression, even asymptomatic pregnant patients with *Strongyloides* infection should be treated. The mortality rate is very high in cases of overwhelming autoinfection, and prompt diagnosis and treatment may be lifesaving (7). Toxicity is a major problem with thiabendazole. Nearly one third of individuals develop nausea, dizziness, pruritus, drowsiness, and headache (5). In addition, visual disturbances, tinnitus, hyperglycemia, hypotension, hepatic dysfunction, and severe hypersensitivity reactions may occur. Ivermectin appears to be safe in pregnancy (21). Albendazole is a less expensive alternative but is not as effective as ivermectin (21).

Trichuriasis

Trichuris trichiura, the whipworm, is one of the most prevalent helmintic infestations, with approximately 800 million infected individuals worldwide (1,7,22). In the United States, approximately 2.2 million people are infected with *Trichuris* (3,22). This parasite resides in the cecum and ascending colon. Man is the principal host, and infection is acquired by ingesting embryonated eggs (7). No extraintestinal migration

of larvae occurs in the life cycle of *T. trichiura*.

The majority of infected persons have low numbers of *Trichuris* and are asymptomatic (7). However, heavy infestation can occur (especially in children) and is associated with anemia, bloody diarrhea, abdominal pain, and malaise (7,22,23). Severe infection with dysentery and tenesmus may result in rectal prolapse (7). Other than iron deficiency anemia or malnutrition in association with heavy infestations of whipworms, *Trichuris* is not a significant threat to pregnant women or their fetuses.

Diagnosis is made by demonstrating the characteristic lemon-shaped ova on a smear of fecal material. The treatment of choice is mebendazole (Vermox) 100 mg twice per day for 3 days or 500 mg once (Table 22.9). Mebendazole is poorly absorbed and thus has very few side effects (7). A single dose of albendazole 400 mg may be used as an alternative. However, unless severe infection with significant anemia, malnutrition, and/or rectal prolapse is present, treatment of pregnant women should be delayed until after delivery.

Tissue Nematodes

Filariasis

Filarial infection is present in over 100 million people worldwide (24). The seven filarial parasites that infect humans, their distribution, their vectors, and their major clinical presentations are given in Table 22.10.

Parasite	Distribution	Vector	Clinical Manifestations
Wuchereria bancrofti	Tropics worldwide	Mosquito	Lymphatic obstruction Pulmonary (eosinophilia) Asymptomatic (microfilaremia)
Brugia malayi	Asia	Mosquito	Lymphatic obstruction Pulmonary (eosinophilia) Asymptomatic (microfilaremia)
Onchocerca volvulus	Africa, Central and South America	Black fly	Dermal (pruritus, papulelichenification) Ocular (keratitis, posterior lesions) Asymptomatic (microfilaremia)
Loa loa	Africa	Tabanid fly	Dermal (angioedema, pruritus) Ocular (subconjunctival worm) Asymptomatic (microfilaremia)
Mansonella streptocerca	Africa	Midge	Dermal (pruritus, papules, lichenification) Asymptomatic (microfilaremia)
Mansonella perstans	Africa, South America	Midge	Dermal (angioedema) Constitutional (headache, arthralgia) Asymptomatic (microfilaremia)
Mansonella ozzardi	Central and South America	Midge	Dermal (pruritus) Constitutional (arthralgia, headache) Asymptomatic (microfilaremia)

TABLE 22.10. FILARIAL PARASTIES AND THEIR CLINICAL MANIFESTATIONS

Bancroftian and Brugian Filariasis

Bancroftian filariasis and brugian (Malayan) filariasis are similar clinical entities caused by *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori* (25). An estimated 120 million people are infected with these parasites (25). *Wuchereria bancrofti* is found throughout the tropics and subtropics; *B. malayi* is present in South and

Southeast Asia; and *B. timori* is limited to the eastern Indonesian archipelago (25).

Following the bite of an infected vector, infective larvae pass into the lymphatics and lymph nodes, where they mature into adult worms. Fertilized female filariae discharge microfilariae into the bloodstream, where they circulate or migrate to the skin. With the exception of *W. bancrofti* in patients from the South Pacific, a surge of microfilariae into the bloodstream occurs at night. Microfilariae can invade the placenta and fetus (26,27), especially in deliveries occurring during the night (17). Carayon et al. (28) reported the presence of chronic bancroftian filariasis in the fallopian tubes or ovaries, with resultant infertility.

In lymphatic filariasis (caused by *W. bancrofti* and *B. malayi*), the clinical findings are due to either acute inflammation or chronic lymphatic obstruction. Lymphadenopathy may be the only manifestation of the infection, or edema and ultimately elephantiasis may occur (25). If lymphatics rupture into body cavities, the patient may present with chyluria, chylothorax, or chylous ascites. If elephantiasis involves the breast, it may interfere with lactation; if the vulva is involved, labor may be obstructed (4). In addition *W. bancrofti* and *B. malayi* cause the hyperresponsive tropical pulmonary eosinophilia syndrome. Most commonly, *W. bancrofti* and *B. malayi* result in asymptomatic disease with microfilaremia. The frequent presence of renal abnormalities in microfilaremic patients with filariasis due to *W. bancrofti* has been demonstrated (24).

Definitive diagnosis of filariasis depends on demonstrating the parasite in either blood or tissue. Blood samples should be obtained around midnight, except in patients from the South Pacific in whom a nighttime surge of microfilariae into the blood does not occur (24,25). The blood smear is stained and examined for microfilariae. Adult worms can be demonstrated occasionally in lymph node biopsies. Although serologic tests are available, they do not differentiate the various types of filariasis, nor do they distinguish current from past infection (25). PCR tests for detection of *W. bancrofti* in blood have been developed (29).

No totally satisfactory treatment for filariasis exists (25). Diethylcarbamazine (Hetrazan) is the drug of choice for bancroftian and brugian filariasis (Table 22.9) (13,25). The following dosage schedule is recommended: day 1: 50 mg orally; day 2: 50 mg three times a day; day 3: 100 mg three times a day.; days 4 to 14: 2 mg/kg three times a day (13). Diethylcarbamazine reduces the number of microfilariae in the blood. It kills some but not all adult worms (25). However, when it kills worms, an acute inflammatory response occurs that results in a granulomatous process and fibrosis (25). Ivermectin in a single dose of 200 to 400 µg/kg has a similar antimicrofilarial action (25). Acute inflammatory reactions are treated with antiinflammatory agents. Surgery is rarely indicated for patients with elephantiasis of the legs (25).

Loiasis

Loiasis is caused by the parasite *Loa loa,* which is transmitted to humans by the tabanid flies. *Loa loa* is irregularly distributed in West and Central Africa, where the vectors, diurnally biting flies (*Chrysops* sp) live in the rain forest canopy (25).

Although many patients infected with *L. loa* are asymptomatic, they have high

eosinophil levels (25). Loiasis is clinically characterized by transient subcutaneous swellings called Calabars. The onset of these swellings often is preceded by localized pain and pruritus (25). Usually only a single swelling occurs at a time and lasts for several days to weeks. However, infected visitors to endemic areas may develop a hyperreactive state, with frequent recurrences of swellings, greater eosinophilia, increased ®FN1¯debilitation, and more complications, especially renal disease (25).

Loiasis should be suspected when a patient from West or Central Africa presents with a typical clinical picture. Diagnosis is confirmed by demonstrating microfilariae on blood smears obtained during daytime.

Diethylcarbamazine is the drug of choice for *L. loa* (Table 22.9) (14). Although it eliminates microfilariae from the blood, diethylcarbamazine often does not kill adult worms (25,30). Dosing is similar to that described for bancroftian and brugian filariasis (Table 22.9). Concomitant administration of antihistamines or corticosteroids is recommended to decrease allergic reactions due to disintegration of microfilariae (14). In patients with high microfilarial loads, rapid killing of microfilariae may precipitate encephalopathy (14,25,31). Alternatively, ivermectin as a single dose of 200 µg/kg reduces the load of microfilariae in the peripheral blood (32). However, in patients with high microfilarial counts (>30,000/mL) fever, pruritus, headache, and arthralgias often occur within 36 hours after ivermectin administration (14,25). Albendazole 200 mg orally twice a day for 3 weeks has been shown to slowly reduce microfilarial levels by exerting an embryotoxic effect on the adult worms (33).

Onchocerciasis

Onchocerciasis (river blindness) is caused *by Onchocerca volvulus,* which is transmitted to humans by black flies.

Onchocerca volvulus (onchocerciasis) presents most commonly as a papulonodular dermatitis. However, the most devastating presentation of onchocerciasis is blindness due to the damage in the eye (keratitis, chorioretinitis) produced by the microfilariae of *O. volvulus.* Twenty million people are infected with *O. volvulus* in West, Central, and East Africa, and an additional one million people are infected in South and Central America (25).

Diagnosis is made by demonstrating microfilariae in skin snips or in the cornea or anterior chamber of the eye on slit-lamp examination (25). Demonstrating adult worms in biopsy specimens of the nodules also can be used (25). When the diagnosis is strongly suspected but parasites cannot be identified, the diagnosis can be confirmed if a single oral test dose of 50 mg of diethylcarbamazine produces exacerbation of the rash (Mazzotti reaction) (25).

In the past, diethylcarbamazine was the preferred treatment for onchocerciasis. However, later studies demonstrated that ivermectin is safer and more effective than diethylcarbamazine for the treatment of *O. volvulus* infections (14,25). Ivermectin is currently considered the drug of choice (14); however, like diethylcarbamazine, ivermectin does not kill adult worms. Thus, repeated courses of treatment with 150 mg/kg every 6 to12 months is recommended (Table 22.9) (14). With this approach,

embryogenesis to the microfilarial stage is prevented, resulting in slow but steady attrition of adult worms (25). Ivermectin therapy causes marked decreases in microfilariae in the anterior chamber of the eye, thus leading to improvement is severe skin lesions and healing of early lesions in the anterior eye (25). Annual treatments with ivermectin 150 µg/kg have been shown to prevent blindness due to ocular onchocerciasis (34).

Mansonella Infections

Mansonella ozzardi occurs in Latin America and is transmitted by blackflies and midges. Adult worms reside in visceral fatty tissues, and the microfilariae are found in peripheral blood (nonperiodic) (25). The overwhelming majority of patients are asymptomatic. *Mansonella perstans* is found in Africa and South America and is transmitted by midges. The adult worms reside in body cavities, and the microfilariae are found in peripheral blood, especially at night (25). Although most patients are asymptomatic, conjunctival nodules may be present (35). I>Mansonella streptocerca is found in central Africa and is transmitted to humans by midges (25). *Mansonella streptocerca* produces a disease characterized by dermatitis, and the microfilariae are found in skin snips (25).

Mansonella perstans and *M. ozzardi* have been referred to as nonpathogenic, because so many infected individuals remain asymptomatic. However, they have been associated with arthralgias and constitutional or neurologic symptoms. *Mansonella streptocerca* presents as a papulonodular dermatitis. All *Mansonella* infections require treatment. Diethylcarbamazine has no effect on *M. ozzardi* (14). Ivermectin mg/kg as a single dose has been shown to be effective in treating *M. ozzardi* (14,36). The drug of choice for *M. perstans* is mebendazole 100 mg twice a day for 30 days (14). Although an FDA-approved drug, mebendazole is considered investigational by the FDA for this indication. Ivermectin 150 mg/kg as a single dose or diethylcarbamazine 6 mg/kg/day for 14 days are the drugs of choice for treatment of *M. streptocerca* infection (14). Ivermectin is safe for use in pregnancy.

Trichinosis

Trichinella spiralis, the parasite that causes most human infection, is widespread throughout temperate areas of the world, especially where pork is a major component of the diet. Trichinosis occurs when inadequately cooked meat contaminated with infective larvae of *Trichinella* sp is eaten (25). Five species have now been described for the genus *Trichinella* based on genetic, biochemical, and biologic data (25). Human infection rarely is caused by *Trichinella britoui, Trichinella nativa,* and *Trichinella nelsoni* and only a single case of human infection with *Trichinella pseudospiralis* has been reported (25). Fortunately, most swine in the United State are fed grain and thus are uninfected. Thus, fewer than 100 cases of trichinosis are reported annually in the United States; approximately 75% are due to inadequately processed pork and the rest from poorly cooked bear meat, walrus meat, or cougar jerky (25).

The larvae are ingested in an encystic form in muscle and are freed from the cyst by acid pepsin digestion in the stomach. Once the larvae reach the duodenum and jejunum, they attach to the mucosa and mature into adult worms. The adult forms of *Trichinella* penetrate the intestinal mucosa to begin discharging larvae (25). The newborn larvae enter the bloodstream from where they invade striated muscles.

After burrowing into the muscle, the larvae encyst and become infective. Over the next several months, the cyst calcifies.

The major reservoir for *T. spiralis* is the pig. Restrictions on methods of feeding used by commercial hog feeders has significantly decreased this source, and recent epidemics of trichinosis in the United States have been traced to meat obtained from game animals, such as bear, walrus, and cougar (25).

The most common type of trichinosis infection is asymptomatic infestation. With larval invasion of the intestinal wall, nausea, vomiting, diarrhea, and abdominal pain occur. During the period of larval migration, fever and eosinophilia develop. With larval invasion of muscle, patients present with fever, myalgia, periorbital edema, splinter hemorrhages, and rash.

Diagnosis of trichinosis should be suspected in patients presenting with periorbital edema, myositis, and fever. Elevated creatine phosphokinase and lactic dehydrogenase levels are present secondary to muscle involvement. Serologic tests are available (bentonite flocculation) but the results are not positive during the early stages of disease (25). Demonstration of encysted larvae in a muscle biopsy is diagnostic but usually not necessary.

There is no completely effective therapy for trichinosis. Thiabendazole 25 mg/kg twice a day for 7 days (maximum 3 g/day) is effective against ingested larvae; if given within 24 hours of ingestion of meat contaminated with *T. spiralis*, it may prevent trichinosis or reduce its clinical severity (Table 22.10) (25). For later stages, supportive care with rest and salicylates is recommended. In severe disease, corticosteroids may be used to depress the inflammatory response. The efficacy of thiabendazole for trichinosis has not been established. It is effective during the intestinal phase, but has little effect on muscle larvae (24,25). Mebendazole 200 to 400 mg three times a day for 3 days, then 400 to 500 mg three times a day for 10 days may be effective against tissue forms of *T. spiralis* (14). Albendazole at a dose of 400 mg/day for 5 days or flubendazole (not available in United States) also may be effective (14). The most effective means of prevention of trichinosis is proper cooking at 55°C or higher.

Dracunculiasis

Dracunculiasis (guinea worm infection) is caused by *Dracunculus medinensis,* which is ingested by drinking water contaminated with infected crustaceans (25). Larvae are released in the stomach and pass into the small intestine. They then penetrate the mucosa and ultimately reach the retroperitoneum, where they mature and mate. The female worm migrates to subcutaneous tissue, most commonly of the legs (25). The overlying skin ulcerates, producing a chronic cutaneous ulcer from which the worm protrudes. When water is contacted, the worm releases large numbers of larvae, thus completing the life cycle when it is ingested by crustaceans.

Dracunculus medinensis is found predominantly in tropical Africa, especially in areas where people bathe or wade in water used for drinking (25). Usually there are no clinical symptoms or signs until the adult worm reaches the skin where the chronic ulcer develops. Diagnosis usually is made clinically, but larvae can be seen on

microscopic examination of discharge fluid from the ulcer site.

The drug of choice for treatment is metronidazole 250 mg three times a day for 10 days (14). Although it has no direct effect on the worms, metronidazole decreases inflammation and thus facilitates removal of the worm. Thiabendazole 25mg/kg twice a day for 2 days has been used with a similar effect (25). Mebendazole 400 to 800 mg/day for 6 days has been reported to kill the worms directly (14), but its use is discouraged by some authors (25).

Trematodes (Flatworms Or Flukes)

Schistosomiasis

Schistosomiasis is one of the most widespread parasitic diseases, infecting over 200 million people (37,38). Approximately 200,000 deaths per year are attributed to *Schistosomiasis.* It is estimated that in the United States there are over 400,000 individuals with *Schistosomiasis,* almost all of whom came from endemic areas. There are five human blood flukes that cause schistosomiasis: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi,* and *Schistosoma intercalatum.* They have complex life cycles that involve aquatic snails as intermediate hosts. The schistosomes differ from other trematodes in that they exist as separate sexes and infect man by free-living cercariae (38).

Each of the schistosome species has a specific geographic distribution that is determined by the snail host. *Schistosoma mansoni* occurs in Africa, Arabia, South America, and the Caribbean. *Schistosoma haematobium* is found in Africa and the Middle East. *Schistosoma japonicum* is limited to China, Japan, Indonesia, Thailand, and the Philippines. *Schistosoma mekongi* occurs in Southeast Asia, and *S. intercalatum* is found in West Central Africa. In these endemic areas, most infected persons carry a low worm burden. However, the small proportion of the population with a heavy worm burden determines the prevalence and degree of morbidity associated with schistosomiasis (38).

Man is the principal definitive host for these parasites (Fig. 22.4) (38). Following mating of adult worms, eggs are passed outside via host excreta. The eggs hatch in fresh water, where they release ciliated motile miracidia that penetrate into the body of their intermediate host—the snail. For each species and geographic strain, there is a specific snail host. The miracidia multiply asexually inside the snail and emerge as motile cercariae that are the infective form. The cercariae, the free-swimming larval forms, penetrate human skin within 2 minutes of contact. Subsequently, they change into schistosomula, enter the bloodstream, and migrate to the lungs and liver. They mature into adult schistosomes and descend via the venous system to their final habitat (38). *Schistosoma mansoni, S. japonicum, S. mekongi,* and *S. intercalatum* inhabit the mesenteric and portal veins. *Schistosoma haematobium* inhabits the pelvic and bladder venous plexuses. In these locations, adult worms produce eggs that migrate to the bladder or intestinal tract lumen.

FIGURE 22.4. Life cycle of schistosomes. (From Miller LH. Plasmodium species. In: Mandell GL, Douglas RG, Bennett JE, eds. *Principles and practice of infectious disease*. New York: John Wiley & Sons, 1979, with permission.)

There are three major disease syndromes that occur in schistosomiasis: dermatitis, Katayama fever, and chronic fibroobstructive sequelae. The serious impact on public health associated with schistosomiasis is the result of chronic infection that results from the granulomatous immune response of the human host to the eggs produced by the schistosomes and subsequent fibrous scarring (38,39). Disease severity is proportional to the intensity and duration of infection.

Acute schistosomiasis first presents as dermatitis within 24 hours of skin penetration by the cercariae. It is a pruritic papular skin rash commonly called “swimmer's itch.” The dermatitis is thought to be a sensitization reaction and does not occur with primary exposure (38). With commencement of ova production 4 to 8 weeks following infection, schistosomiasis is manifested by acute onset of fever, chills, sweats, headache, cough, and malaise. This condition is known as Katayama fever. *Schistosoma mansoni* and *S. japonicum* produce diarrhea with blood and mucus, weight loss, abdominal pain, and hepatosplenomegaly. The symptoms and signs of Katayama fever usually resolve within a few weeks, but occasionally death occurs, especially in acute schistosomiasis with *S. japonicum* (38).

The majority of persons infected with schistosomiasis have a low-to-moderate worm burden and remain asymptomatic chronic cases (38). When heavy worm infestation is present, the characteristic chronic sequelae of schistosomiasis ultimately occur. The host response is to develop a granuloma around each egg (38,39). With resolution of this lesion, collagen deposition and fibrosis occur, thus producing clinical disease (40). Chronic schistosomiasis caused by *S. japonicum, S. mansoni,* and *S. mekongi* presents with fatigue and colicky abdominal pain associated with intermittent diarrhea (38). The intestines and liver are the sites most commonly affected. Chronic intestinal disease is characterized by Banti syndrome or polyposis of the colon. The end stage of hepatic schistosomiasis presents with jaundice, ascites, and liver failure. Infection with *S. haematobium* is characterized by hematuria during the acute phase, and the chronic stage is associated with obstruction of urine flow and polyposis (38). The end stage is characterized by hydronephrosis, infections, and uremia. Malignant changes in the bladder occur in

some endemic areas (41).

The female genital tract can be infected with eggs of *S. mansoni* and *S. haematobium* (42,43 and 44). Rosen and Kim (45) noted that acute and chronic schistosomiasis inflammation of the fallopian tube can result in ectopic pregnancies and infertility. Inflammation of the cervix, vagina, and vulva may occur and interfere with coitus, fertility, or ability to deliver vaginally (46). The frequency of placental infection is high in endemic areas, but the infestations are light and associated with little inflammatory reaction (47,48). There is no evidence that placental schistosomiasis is associated with IUGR or preterm delivery (47).

Diagnosis of schistosomiasis should be suspected in patients with the characteristic clinical findings and a history of travel to an endemic area. A definitive diagnosis requires demonstration of schistosome eggs in feces or urine or in tissue obtained by biopsy of the rectum, bladder, or liver. Quantitative assessment of stool and urine specimens is recommended to determine the intensity of infection (38). Serologic tests using immunodiagnostic methods and purified worm antigens are used to screen travelers and immigrants from endemic areas. However, these tests are unable to distinguish new from old infection. Assays for detecting antigens elaborated by adult worms appear to be useful for distinguishing active from inactive infection.

Three drugs currently are available for treatment of schistosomiasis (Table 22.10): praziquantel, oxamniquine, and metrifonate. Praziquantel is acknowledged as the drug of choice for all species of schistosomes. This drug causes spastic paralysis of the worms and damage to the outer tegument of the worm. The recommended dose of praziquantel depends on the species involved: *S. haematobium* and *S. mansoni* 40 mg/kg/day in two doses for 1 day; and *S. japonicum* and *S. mekongi* 60 mg/kg/day in three doses for one day. However, praziquantel is expensive; thus, oxamniquine and metrifonate are used in developing countries (14). Oxamniquine is effective against *S. mansoni* infection and is recommended as a single dose of 15 to 20 mg/kg. In Egypt and East Africa, doses up to 60 mg/kg over 2 to 3 days are required (14). This drug is contraindicated in pregnancy. Metrifonate is effective against *S. haematobium* at a dosage of 7.5 mg/kg orally repeated twice at 2-week intervals.

Opisthorchiasis

Opisthorchiasis is caused by the liver flukes *Opisthorchis viverrini* and *Opisthorchis felineus.* These are common liver flukes in dogs and cats that can be transmitted to humans (38). The adult worms are primarily located in the bile ducts and gallbladder, where they cause irritation and trauma to the epithelial cells of the biliary tract that lead to adenomatous formation. Periductal infiltration of inflammatory cells and fibrosis ultimately occur and lead to obstruction of the bile duct (49).

The majority of individuals infected with opisthorchiasis are asymptomatic. With mild disease, intermittent episodes of dull pain and discomfort are present in the right upper quadrant. As the disease progresses, the symptoms become persistent. In addition, a hot sensation is noted in the abdominal skin. Rarely patients develop cholangiocarcinoma and relapsing cholangitis.

Diagnosis of opisthorchiasis requires identification of the characteristic eggs in the stool, duodenal aspirate, or bile. Praziquantel is the drug of choice at a dosage of 25 mg/kg given three times in a single day. Alternatively, a single dose of 40 to 50 mg/kg can be used for logistic reasons with mass therapy programs. Other drugs include albendazole 400 mg twice a day for 7 days (63% cure rate) or mebendazole 30 mg/kg for 20 to 30 days (89% to 94% cure rate).

Clonorchiasis

Clonorchis sinensis, the Chinese or oriental liver fluke, is the etiologic agent for clonorchiasis. Adult flukes inhabit distal biliary capillaries. Millions of individuals in China, Hong Kong, Vietnam, and Korea are infected with this parasite. Most infections are asymptomatic. Progressive disease results in biliary obstruction. Individuals infected with large numbers of *C. sinensis* may rarely develop cholangitis. This infection has been associated with cholangiocarcinomas.

The diagnosis is made by demonstrating the eggs of *C. sinensis* in stool. Praziquantel 25 mg/kg three times a day for 1 to 2 days is very effective (cure rates 85% to 100%, respectively). Albendazole is an effective alternative drug at a dosage of 5 to 10 mg/kg twice a day for 7 days.

Fascioliasis

The sheep liver fluke *Fasciola hepatica* causes fascioliasis. Clinically, this disease has two stages. In the acute or migratory phase, immature flukes are present in the liver. Patients develop fever, abdominal pain (right upper quadrant), loss of appetite, nausea, flatulence, and diarrhea. Repeated attacks of urticaria with or without wheezing occur. Once the flukes penetrate into the bile ducts, the acute symptomatology recedes. After several years, the adult flukes cause inflammation and obstruction in the bile ducts, resulting in a clinical presentation with cholangitis or cholecystitis.

Fascioliasis is diagnosed by demonstrating the eggs of *F. hepatica* in the stool or duodenal aspirate. Praziquantel is ineffective. The recommended treatment is bithionol 30 to 50 mg/kg on alternate days for 10 to 15 doses (14). Alternatively, trichlabendazole 10 mg/kg as a single dose may be given (14).

Paragonimiasis

Paragonimiasis is caused by many species of *Paragonimus,* the lung flukes. The most common is *Paragonimus westermani*, the oriental lung fluke. The degree of infection and symptomatology depend on the worm burden and the location of infection. There is an initial, acute phase during the period of invasion and migration of the immature flukes characterized by diarrhea, abdominal pain, and urticaria, followed in a few days by fever, chest pain, cough, dyspnea, malaise, and night sweats (31). Chronic disease is either pulmonary or extrapulmonary (cerebral, abdominal, and subcutaneous).

Pulmonary paragonimiasis presents with a dry cough that produces a tenacious, rust- or golden-colored sputum. Hemoptysis is common in advanced disease.

Untreated infection may progress to bronchiectasis. Cerebral paragonimiasis is common in children. It presents initially as meningoencephalitis but progresses to a chronic stage characterized by signs and symptoms of a space-occupying lesion in the brain.

Diagnosis of paragonimiasis relies on a high index of suspicion in individuals with characteristic symptoms of chronic bronchitis or hemoptysis who came from endemic areas in West Africa, the Far East, India, and Central and South America. Eosinophilia is commonly present in the early stage. Recovery of the eggs from sputum, feces, or pleural fluid confirms the diagnosis. An ELISA immunodiagnostic test has been introduced that is highly specific for *Paragonimus* infections (50). Praziquantel is the drug of choice for paragonimiasis at a dosage of 25 mg/kg three times a day for 2 to 3 days (14). An alternate drug is bithionol 30 to 50 mg/kg on alternate days for 10 to 15 doses (14).

Cestodes (Tapeworms)

Tapeworms are capable of producing human disease in either stage of their life cycle (51). The adult stage produces signs and symptoms related to the gastrointestinal tract, where the adult worm lives. The larval stage produces signs and symptoms secondary to enlarging larval cysts in various tissues.

Humans are the definitive hosts for the tapeworms causing gastrointestinal symptoms. There are four of these tapeworms: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana* (dwarf tapeworm). The only larval stage man supports, among the cestodes, is *Echinococcus granulosis.* Human infection occurs when raw or undercooked meat containing the larvae of the tapeworms is ingested.

Taenia Saginata *(Beef Tapeworm)*

Man is the only definitive host of *T. saginata*. Following ingestion of infectious larval cysts in raw or inadequately cooked beef, the larva is released, develops into an adult worm, and attaches to the intestinal wall. This tapeworm can grow to over 30 feet in length. Symptoms due to *T. saginata* are limited and involve abdominal cramps and malaise (33). The diagnosis is made by examining the stool for proglottids. The drug of choice for treatment is praziquantel 5 to 10 mg/kg (Table 22.10). Niclosamide is an alternative given as a single dose of 2 g. During pregnancy, treatment can be withheld until after delivery.

Taenia Solium *(Pork Tapeworm)*

Man is either an intermediate or definitive host for this parasite (51). Infectious larval cysts are acquired by ingesting inadequately cooked infected pork and develop into the adult form, the pork tapeworm, which resides in the intestinal tract. *Taenia solium* reaches a length of 10 to 20 feet. Clinical manifestations of intestinal pork tapeworm infection are mild or nonexistent (51). Diagnosis relies on detection of *T. solium* eggs on stool examination. The treatment of choice is praziquantel 5 to 10 mg/kg in a single dose. Niclosamide in a single 2-g dose is an alternative treatment. In pregnant women, treatment can be delayed until after delivery. Cysticercosis is an infection caused by the larval stage of the pork tapeworm, *T. solium*. The infection is acquired

by ingesting the eggs of *T. solium.* Although subcutaneous and intermuscular tissues are the most common sites for cysticerci, neurocysticercosis is the most important clinical manifestation (51,52). If visible cysts are demonstrated in the brain parenchyma, albendazole or praziquantel is recommended. Albendazole 400 mg twice a day for an 8- to 30-day course is the optimum therapy (Table 22.10) (14). Alternatively, praziquantel 50 mg/kg/day in three doses for 15 days can be used but appears to be less effective (3,52). Corticosteroids should be given for 2 to 3 days before and during therapy for neurocysticercosis (13). Some authorities question the efficacy of antihelmintic therapy for neurocysticercosis and recommend corticosteroids alone (51).

Diphyllobothrium Latum *(Fish Tapeworm)*

Diphyllobothriasis occurs as the result of ingesting uncooked freshwater fish. The adult fish tapeworm reaches lengths of 40 to 50 feet. Infection usually is asymptomatic, but occasionally nonspecific symptoms such as weakness, dizziness, salt craving, diarrhea, and intermittent abdominal pain occur. *Diphyllobothrium latum* has the greatest chance to adversely affect pregnancy (4). It competes with its human host for folic acid and vitamin B_{12}; in pregnancy, this may result in megaloblastic anemia. Diagnosis is made by demonstrating proglottids or eggs in feces. Pregnant women with anemia due to *D. latum* should receive vitamin B_{12} and folic acid. Praziquantel 5 to 10 mg/kg as a single dose is the treatment of choice. In pregnancy, treatment can be delayed until after delivery.

Hymenolepis Nana *(Dwarf Tapeworm)*

Man acts as both the definitive and intermediate host for *Hymenolepsis nana.* It is the only tapeworm that can be transmitted from human to human (51). The adult worm is 1 to 2 inches in length, thus the name dwarf tapeworm. The clinical symptomatology manifests as abdominal cramps and diarrhea. Diagnosis is confirmed by demonstrating the eggs of *H. nana* in stool. The drug of choice for *H. nana* is praziquantel 25 mg/kg as a single dose. The alternate regimen consists of niclosamide as a single dose of 2 g, followed by 1 g/day for 6 days. During pregnancy, treatment can be delayed until after delivery.

Echinococcus Granulosis *(Hydatid Disease)*

Humans are accidental intermediate hosts of *Echinococcus* sp, the carnivore tapeworms. Echinococcosis has two forms: hydatid or unilocular cyst disease caused by *Echinococcus granulosus,* or *Echinococcus vogeli*; and alveolar cyst disease caused by *Echinococcus multilocularis* (51). Following ingestion of eggs, larvae penetrate into the mesenteric vessels and are carried to multiple organs. The liver and lungs are the most common sites for development of large hydatid cyst(s). The hybrid cysts of *E. granulosus* usually form in the liver (50% to 70% cases) or lung (20% to 30% cases) (51). Symptoms often are absent and the cysts are recognized incidentally. Symptoms, if present, are the result of the mass effect of enlarging cysts (51). Diagnosis is suggested by the presence of a cystic mass and eosinophilia in a patient from an endemic area (51). Infection suspected with imaging studies can be confirmed by specific ELISA and Western blot serology that is available in the United States through the CDC (51).

For hydatid cysts due to *E. granulosus,* the drug of choice is albendazole 400 mg twice a day for 28 days and repeated as necessary (14). In some patients, surgical excision of cysts may be necessary (53). Some authorities suggest that surgical resection is the optimal treatment of symptomatic cysts (51). Praziquantel may be useful preoperatively or in case of spill during surgery (14). Percutaneous drainage with ultrasound guidance plus albendazole therapy has been shown to be effective for management of hepatic hydatid cyst disease (54). With *E. multilocularis,* surgical excision is the only reliable means of treatment (14). Reports have suggested that albendazole or mebendazole may be useful in this scenario (14).

CHAPTER REFERENCES

General

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ANTIMICROBIAL AGENTS

Because bacterial infections play a prominent role in obstetrics and gynecology, antimicrobial agents are among the most frequently administered drugs. Confronted with an extensive and expanding array of antibiotics, the clinician must be well versed in use of antibiotics in the day-to-day care of patients. Moreover, practice habits have changed as we have seen developments in home parenteral therapy, new antibiotics, and new dosing regimens (as for gentamicin). A further concern is the development of antibiotic-resistant bacteria (1,2,3 and 4).

MODE OF ACTION OF ANTIBIOTICS (5,6)

Antibiotics exert inhibitory effects on bacteria by interfering with their metabolic activities or the function of their structural components. This inhibition is dose related and requires the administration of effective inhibitory concentrations of the agent without reaching toxic levels. A bacterial species is considered sensitive to an antimicrobial agent if the organism is inhibited by concentrations of the antibiotic that can be obtained without harm to the host. Ideally, the action of an antibiotic should be directed against bacterial, not human, processes, thus avoiding toxicity for the host.

Antimicrobial agents may interfere with bacterial metabolism, the synthesis or integrity of structural components (e.g., cell wall or plasma membrane), and biosynthesis of proteins and nucleic acids. In general, the metabolic activities of bacteria are similar to those of mammalian cells. However, in some cases, the bacteria synthesize certain compounds that animal cells must obtain as preformed molecules. Folic acid is an example of such a compound. Thus, the inhibition of folate biosynthesis affects bacterial cells selectively. In addition, bacteria require a cell wall to protect them from osmotic damage, which provides them with a characteristic shape. Because a cell wall is not present in mammalian cells, it is a selective target for antibiotic action. The cell membrane, which lies inside the cell wall, is another site where antibiotic action may be demonstrated. The bacterial

plasma membrane has essentially the same structure as the cell membrane of mammalian cells. As a result, antibiotics that are active against the bacterial cell membrane are usually relatively toxic for the host. Bacterial protein synthesis occurs on 70S ribosomes within the cell. Mammalian ribosomes (except in mitochondria) are 80S entities, and this difference may account for some selective action of antibiotics that inhibit protein synthesis. Nucleic acid synthesis by bacteria also offers a possible site for antibiotic action.

Antibiotics are classified as bactericidal or bacteriostatic on the basis of their mode of action. Bactericidal drugs produce a change in the bacterial cell that is incompatible with survival. Examples of such changes include disruption of the cell wall structure or disorganization of the cell membrane. Drugs are considered bacteriostatic if they inhibit certain metabolic events and thus cause suspension of bacterial growth. This blockade of metabolic activity is not immediately lethal, and if the antibiotic is removed from the environment, growth may resume. The sites in bacteria where antibiotics can exert their action are summarized in Table 23.1. Bacterial resistance to antibiotics occurs commonly, with consequences including prolonged hospital stays, increased costs, and increased risk of death (4). Bacteria may be naturally resistant to an antibiotic (as *Escherichia coli* is to penicillin G) or may acquire resistance (as *E. coli* does to ampicillin). Most often, acquired bacterial resistance results from a change in the drug target, production of a detoxifying enzyme, or decreased antibiotic uptake.

TABLE 23.1. MECHANISM OF ACTION OF ANTIMICROBIAL AGENTS

Changes in the drug target may involve decreasing the receptor affinity or substituting a different pathway. Changes in uptake may occur by decreasing permeability or increasing efflux through an active system. Mechanisms of resistance may develop by mutation, with resistance genes commonly carried on extra chromosomal plasmids. These can be transferred among individual bacterial cells by conjugation, transduction, or transformation.

PHARMACOKINETIC CONSIDERATIONS IN OBSTETRIC PATIENTS

For detailed discussion of pharmacokinetic considerations, see references 5, 7, 8

and 9. It is estimated that 25% to 40% of pregnant women are exposed to antimicrobial agents. Pertinent to this chapter are two general pharmacokinetics considerations: the effect of pregnancy on serum antibiotic levels and the distribution of antibiotics into the fetal compartment and into breast milk.

Effect of Pregnancy on Serum Antibiotic Levels

Antimicrobials may be administered during pregnancy to treat a coincidental maternal infection, such as pneumonia or pyelonephritis; to treat a maternal-fetal infection, such as syphilis or chorioamnionitis; or to treat a predominantly fetal infection, such as some cases of toxoplasmosis.

Physiologic alterations that occur in normal pregnancy can result in significant effects on the pharmacokinetics of antimicrobial agents (8). The expanded blood volume (increased by 50%) associated with pregnancy leads to an increased volume of distribution and reduced plasma protein concentration, which results in lower serum concentrations for many antimicrobial agents. Renal blood flow and glomerular filtration rate increase by approximately 50%, with a resultant increase in clearance of antimicrobials excreted via the kidneys. The increased progesterone levels result in activation of hepatic metabolism, decreased gastrointestinal motility, and delayed gastric emptying. As a result of the gastrointestinal effects, orally administered antibiotics may be absorbed in an unpredictable manner during pregnancy. Finally, during pregnancy, a significant percentage of the antimicrobial agent is in the fetal compartment and not available to the mother. The net result of these physiologic changes in pregnancy is a decrease in the amount of drug available and an increase in the dose required. Ironically, the concern regarding maternal and fetal toxicity has often led to the decision to prescribe lower doses of antibiotics. In addition, technical and ethical problems may make the study of antibiotic kinetics more difficult in pregnant than in nonpregnant women.

Lower serum or plasma levels are suspected in pregnancy for a number of antibiotics, and for ampicillin, serum levels have been documented to be lower in pregnancy. Table 23.2 summarizes the effect of pregnancy on antibiotic concentration. Overall, the percentage decrease in levels ranges from 10% to 50%. Decreases in serum ampicillin concentrations have been observed after both oral and intravenous administration. The reasons for the lower levels of antibiotics in pregnant women include rapid excretion, a larger volume of distribution, and sequestration of the drug in the fetal compartment.

Antibiotics for which levels are clearly lower in pregnancy	
Ampicillin	
Penicillin V	
Piperacillin	
Antibiotics for which levels are suspected of being lower in pregnancy	
Methicillin	Amoxicillin–clavulanic acid
Cephalexin	Ticarcillin–clavulanic acid
Cephalothin	Ampicillin–sulbactam
Cephazolin	Piperacillin–tazobactam
Cefoxitin	Gentamicin
Cefamandole	Kanamycin
Cefotetan	Amikacin
Ceftriaxone	Tobramycin
Cefotaxime	Nitrofurantoin
Moxalactam	Erythromycin
Cefoperazone	
Ceftizoxime	
Antibiotics for which levels are probably unchanged in pregnancy	
Pirmecillinam	
Cephaloridine	
Clindamycin	
Thiamphenicol	
Trimethoprim-sulfamethoxazole	

TABLE 23.2. EFFECT OF PREGNANCY ON SERUM ANTIBIOTIC LEVELS

The therapeutic implication of these findings is not altogether clear, because peak blood levels even in pregnancy are usually many times greater than minimal inhibitory or minimal bactericidal concentrations. Further, in pregnant women given standard doses, there have been few documented cases of antibiotic failure due solely to subtherapeutic levels. Accordingly, with agents with wide margins of safety (e.g., ampicillin and cephalosporins), use dosages in the upper ranges or use shorter dosing intervals. For agents with narrower margins of safety (e.g., aminoglycosides), use standard doses (on a milligram-per-kilogram basis). Then, if therapy does not appear adequate, determine antibiotic levels. Remember, however, that the more common causes of antibiotic failure include resistant organisms and abscesses and other masses.

Distribution of Antibiotics

Distribution of drugs into various body fluids depends on whether the mechanism of transfer is active or passive. Passive mechanisms are probably more important for antibiotic transfer, and these mechanisms (mainly diffusion) are influenced by the concentration gradient, molecular weight, binding to protein, and ionization of the drug. In general, rapid transfer is favored by a large concentration gradient, small molecular weight, and low protein binding. The effect of ionization is more complex; only an un-ionized, non–protein-bound drug diffuses across membranes. If all other factors are equivalent, drugs that are weak bases will have a higher concentration in a more acid medium, and drugs that are weak acids will have a greater concentration in a more alkaline medium.

Placental Transfer of Antibiotics

Available clinical experiments on placental transmission of antibiotics have shown that all antibiotics pass into the fetal circulation. Of special importance is the relative inaccessibility of the fetal circulation and, to a lesser extent, the amniotic fluid. Consequently, much of the information comes from “single-dose, single-determination” studies. This is an important limitation because levels of antibiotics in the fetal compartment should increase after repeated regular maternal dosing. In addition, there are likely to be marked differences in transmission at different gestational ages. Thus, data obtained from mid-trimester pregnancies may not be directly applicable to term pregnancies (8).

Despite variation in specifics, most antibiotics have a similar pattern for placental transfer. After a single intravenous infusion into the mother, antibiotic concentrations usually peak in cord blood within 30 to 60 minutes after they peak in maternal serum. The reported fetal : maternal peak serum levels have ranged from 0.3 to 0.9 for ampicillin, carbenicillin, cephalothin, clindamycin, and the aminoglycosides. On the other hand, the ratios for erythromycin and dicloxacillin are less than 0.1. These differences reflect the protein-binding capacity of the antibiotics. Thus, agents that are minimally protein bound (20%), such as ampicillin, reach high levels in the fetus,

whereas those with high binding such as dicloxacillin (96% bound) achieve lower levels in the fetus. Because antibiotic levels in amniotic fluid during the third trimester depend on excretion of antibiotics in fetal urine, there is a delay of several hours after maternal administration before antibiotic levels are detectable in the amniotic fluid (8). This latter finding explains the poor maternal outcome with clinical amnionitis in association with intrauterine death; amniotic fluid antibiotic levels are negligible in association with stillbirths.

Antibiotic Excretion in Breast Milk

Excretion of antibiotics in breast milk is governed by the same principles that regulate placental transmission. In addition to the influence of concentration gradient, molecular weight, and protein binding, differences in pH level between breast milk and serum may be particularly important. Because the pH level of milk (range, 6.4 to 7.6) is usually lower than that of plasma, antibiotics that are weak bases tend to have higher concentrations in the milk. Conversely, antibiotics that are weak bases tend to have higher concentrations in serum. In addition to the concentration of an antibiotic in breast milk, it is necessary to consider the amount of antibiotic consumed by the newborn (i.e., the concentration in milk multiplied by the volume consumed).

Some antibiotics achieve concentrations in breast milk that are from 50% to 100% of serum concentrations. These antibiotics include erythromycin, lincomycin, tetracycline, sulfonamides, chloramphenicol, and isoniazid. More commonly used antibiotics such as penicillin G and oxacillin achieve milk levels that are a smaller percentage of maternal serum concentrations (generally, 2% to 20%). Of the aminoglycosides, data are available for the oldest preparation, streptomycin, which is excreted in small amounts in breast milk for some time after intramuscular administration to the mother.

Any antimicrobial agents that are administered to a lactating mother can be detected in breast milk, but adverse effects on the neonate have only rarely been documented. Most likely, this fortunate circumstance is related to the fairly low drug concentration to which the infant is exposed. In addition, when ingested, some drugs remain unabsorbed or are destroyed in the gastrointestinal tract. It is important for clinicians to recognize that some antimicrobial agents present in breast milk are potentially toxic, particularly in special instances such as prematurity or hereditary deficiencies (Table 23.3).

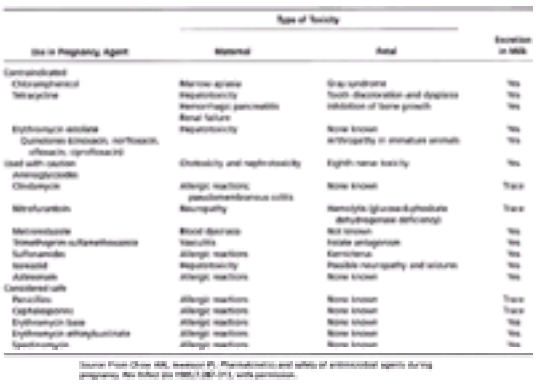


TABLE 23.3. POTENTIAL RISKS ASSOCIATED WITH ANTIMICROBIAL AGENTS

PENICILLINS

Penicillin was initially isolated from the mold *Penicillium notatum* by Fleming in 1929 but was not introduced into clinical practice until 1941. The basic chemical structure of penicillin consists of three components: a thiazolidine ring, the b-lactam ring, and a side chain that largely determines the antibacterial spectrum and pharmacologic properties of each penicillin.

The various semisynthetic penicillins are derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APS). The penicillins can be divided into eight major classes on the basis of their antibacterial activities (Table 23.4).

TABLE 23.4. CLASSIFICATION OF PENICILLINS

Natural Penicillins

The common natural penicillins are penicillin G and penicillin V (penicillin phenoxymethyl). Penicillin G is available as penicillin G potassium, penicillin G sodium, penicillin G procaine, and penicillin G benzathine.

Spectrum of Activity

The penicillins are bactericidal antibiotics that interfere with cell wall formation by affecting the formation of the mucopeptide portion of the cell wall. Penicillin G is active against a wide range of bacteria, predominantly Gram-positive organisms. Among the Gram-positive, facultative, or aerobic cocci, penicillin G is highly active against group A streptococci. Although most *Streptococcus pneumoniae* strains remain extremely sensitive, resistant pneumococcal strains account for about one fourth of all isolates in the United States (1). Group B b-hemolytic streptococci are

sensitive to penicillin G but are approximately tenfold less sensitive than the group A streptococci. In addition, groups C and G b-hemolytic streptococci and the a-hemolytic streptococci such as *Streptococcus viridans* and nonenterococcal group D streptococci are sensitive to penicillin G. The anaerobic Gram-positive cocci such as *Peptostreptococcus* sp are highly susceptible to penicillin G. On the other hand, enterococcal group D streptococci are resistant to penicillin G, as are most *Staphylococcus aureus* strains, whose resistance is due to b-lactamase (penicillinase) production.

Among Gram-positive bacilli, *Corynebacterium diphtheriae, Bacillus anthracis,* and many strains of *Listeria monocytogenes* are sensitive to penicillin G. Anaerobic Gram-positive spore-forming bacilli such as *Clostridium perfringens* and other *Clostridium* sp are penicillin G sensitive. In addition, penicillin G is active against most anaerobic non–spore-forming bacilli such as *Actinomyces, Eubacterium, Bifidobacterium, Propionibacterium,* and *Lactobacillus* species.

Among the Gram-negative cocci, *Neisseria meningitides* remains very sensitive to penicillin G. However, *Neisseria gonorrhoeae* susceptibility has dramatically decreased, so penicillin is no longer a drug used to treat this organism (2). Gram-negative anaerobic cocci such as *Veillonella* sp are also sensitive to penicillin G.

Among Gram-negative bacilli, the Enterobacteriaceae such as *E. coli, Proteus, Klebsiella, Enterobacter, Serratia, Salmonella, Shigella,* and *Citrobacter* spp are resistant to penicillin G. In addition, *Pseudomonas aeruginosa* and other *Pseudomonas* species are resistant to penicillin G. Although penicillin G is active against many Gram-negative anaerobes such as *Fusobacterium* and some *Bacteroides* species, resistant species are *Bacteroides fragilis, Prevotella bivia* (formerly *Bacteroides bivius*), and *Bacteroides disiens.*

Treponema pallidum is sensitive to penicillin G. The mycoplasmas, rickettsiae, fungi, and protozoa are completely penicillin resistant, whereas chlamydiae are relatively resistant.

The spectrum of activity of the phenoxypenicillins—penicillin V, phenethicillin, propicillin, and phenbenicillin—is generally similar to that described for penicillin G. However, penicillin G is more active against streptococci, pneumococci, and *N. meningitides.*

Dosage and Route

Penicillin G is largely destroyed by acid in the stomach, with only about one third of orally administered penicillin G being absorbed. Thus, when oral therapy with penicillin is desired, penicillin V (penicillin phenoxymethyl), because of its greater acid stability, is the usual choice in a dosage of 250 to 500 mg (400,000 to 800,000 units) every 6 to 8 hours. Penicillin V may be given with meals. Based on kinetic studies, Finnish investigators recommended a dose in pregnancy of 1 million units every 6 hours instead of their usual dosing interval of every 8 hours (3).

Crystalline penicillin G is available to be administered intramuscularly or intravenously. When administered intramuscularly, it reaches peak serum

concentrations 15 to 30 minutes after injection; a dose of 1 million units results in a peak serum level of 12 µg/mL. By 3 to 4 hours, serum concentrations are negligible. Crystalline penicillin G is usually given in dosages ranging from 300,000 to 1,000,000 units every 6 hours by the intramuscular route, but it can be given as frequently as every 2 hours. Crystalline penicillin G may be administered intravenously by either intermittent bolus infusion or continuous infusion. The intermittent infusion of high concentrations of penicillin G is generally preferred. A rapid infusion of 5 million units of crystalline penicillin G results in peak serum concentrations of 400 µg/mL within a few minutes. By 4 hours after injection, the serum concentration falls to 3 µg/mL. Intravenous therapy is administered in a dose of 1 million to 5 million units every 2 to 6 hours, depending on the severity of the clinical infection.

Repository penicillins for intramuscular injection are also available; these are penicillin G procaine and penicillin G benzathine. With penicillin G procaine, peak serum levels occur 1 to 3 hours after injection, and detectable levels are usually present for up to 24 hours. The standard dose of penicillin G procaine is 600,000 to 1,200,000 units intramuscularly every 6 to 12 hours. When injected intramuscularly, penicillin G benzathine results in a slow release of penicillin, which lasts for 2 to 4 weeks. After injection of 2.4 million units of penicillin G benzathine, 0.12 µg/mL of penicillin can be detected 14 days after injection. The usual dose is 1.2 million to 2.4 million units, and the interval of dosing depends on the clinical indication.

Side Effects

Although penicillin is one of the least toxic antimicrobial agents, it is commonly responsible for hypersensitivity reactions. These hypersensitization reactions include rash, urticarial reactions, anaphylactic reactions, serum sickness, contact dermatitis, and angioedema. Local reactions may occur such as swelling, pain, and redness at the site of injection or phlebitis after intravenous infusion.

Direct penicillin toxicity may occur with massive doses (60 million to 100 million units daily). Neurologic toxicity with convulsions and coma may result, particularly in patients with renal insufficiency, underlying central nervous system (CNS) disease, or hyponatremia. Interstitial nephritis or hemolytic anemia may occur with large doses of penicillin G. Rarely, administration of penicillin G has been associated with development of thrombocytopenic purpura, glossitis, and stomatitis.

Penicillin V may result in gastrointestinal side effects such as nausea, vomiting, and diarrhea. Hypersensitivity reactions may occur as noted for penicillin G.

Cost

Penicillin G and penicillin V are inexpensive antimicrobial agents. Thus, for microorganisms susceptible to these agents, the penicillins remain the drug of choice.

Use in Pregnancy

Penicillin G rapidly crosses the placenta and achieves levels in cord blood and amniotic fluid. No adverse effects on the fetus have been demonstrated with the use of penicillin G, and this drug is considered safe to use during pregnancy. Similarly,

penicillin V has not been linked with adverse fetal effects.

Metabolism

Penicillin G is primarily excreted in the urine. In patients with normal renal function, more than 70% of the injected dose is excreted within 6 hours. Ninety percent of penicillin G excretion occurs by tubular excretion, and 10% by glomerular filtration. This renal tubular secretion can be partly blocked by probenecid, resulting in a doubling of serum levels of penicillin. Approximately 5% of penicillin G is excreted in the bile. The penicillin not excreted in urine or bile is inactivated in the liver, with penicilloic acid as the major end product. The phenoxypenicillins are also excreted in urine and bile. During the first 6 hours after oral intake, 20% to 40% of the dose of penicillin V can be recovered from urine.

Penicillin G is widely distributed in the body. High concentrations of penicillin G are present in blood, liver, bile, skin, intestines, and kidneys. Low concentrations occur in joint fluid, pericardial fluid, and pleural fluid. Peritoneal fluid contains high concentrations. Small amounts of penicillin G are distributed to brain, nerve, dura, bone marrow, bone, pancreas, adrenal glands, or spleen. Whereas penicillin G poorly penetrates the blood-brain barrier in the presence of normal meninges, when the meninges are inflamed, cerebrospinal fluid (CSF) levels of penicillin G are adequate. Levels of penicillin V are decreased in pregnancy (3).

Indications in Obstetrics and Gynecology

Penicillin G remains one of the most effective antibiotics. Because of its activity against a wide spectrum of bacteria and its safety, penicillin G remains the preferred agent for many clinical infections.

Penicillin G is the drug of choice for infections due to group A b-hemolytic streptococci or group B b-hemolytic streptococci. Because of its activity against aerobic and anaerobic streptococci, *Clostridium* species, and many of the *Bacteroides* species, penicillin G was commonly used in combination with an aminoglycoside as initial therapy for mixed aerobic-anaerobic soft tissue pelvic infections. However, recognition of the role of penicillin-resistant anaerobes has resulted in a diminished role for penicillin G in such infections.

When enterococcal infection is a concern, penicillin G should be added to an aminoglycoside because penicillin plus an aminoglycoside has a synergistic effect on the enterococcus.

As described in Chapter 7 (Sexually Transmitted Diseases), penicillin G in the form of penicillin benzathine is the drug of choice for the treatment of syphilis.

Penicillin G is the drug of choice for the treatment of actinomycosis, which may be found associated with intrauterine device usage. Similarly, it is the drug of choice for clostridial infections. Penicillin G is the recommended drug for prevention of perinatal group B streptococcal infection (4).

Antistaphylococcal Penicillins

The emergence of b-lactamase–producing *S. aureus* led to major efforts for the development of antimicrobial compounds resistant to the hydrolysis of b-lactamase enzymes. This resulted in a large variety of semisynthetic penicillins derived from 6-amniopenicillanic acid. The narrow-spectrum penicillinase-resistant penicillins include methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, and flucloxacillin.

P>***Spectrum of Activity***

Methicillin was the first antistaphylococcal penicillin introduced into clinical medicine. Although it is active against pneumococci and streptococci, its efficacy against these organisms is many-fold less than that of penicillin G. Methicillin is active against most strains of *S. aureus,* but increasingly, methicillin-resistant *S. aureus* (MRSA) has been reported. MRSA is resistant by virtue of altered penicillin-binding proteins. MSRA is also resistant to penicillin G, the cephalosporins, and other penicillinase-resistant penicillins such as nafcillin, oxacillin, cloxacillin, and dicloxacillin. MRSA has been associated predominantly with hospital-acquired infections. In addition, the incidence of methicillin-resistant *Staphylococcus epidermidis* is higher than that for MRSA.

The isoxazolyl penicillins—oxacillin, cloxacillin, and dicloxacillin—have a spectrum of activity similar to that of methicillin. Nafcillin also has a similar antibacterial spectrum. Its stability in the presence of staphylococcal penicillinase is comparable to that of methicillin but greater than that of the isoxazolyl penicillins.

Dosage and Route

Methicillin is administered only by the intravenous route. The dosage can be varied depending on the site and severity of the infection. For infections of moderate severity, 1 g every 4 hours is generally used, and for serious infections such as endocarditis, a dose of 2 g every 2 to 3 hours may be given. After an intravenous injection of 1 g of methicillin, a peak serum level of 60 µg/mL is obtained. There is a rapid fall in serum levels, to 7 µg/mL by 1 hour and less than 1 µg/mL by 2 to 3 hours. The peak level can be doubled by doubling the dose.

Although oral oxacillin is available, it is absorbed erratically. Oxacillin may be given in a dosage of 250 to 500 mg every 4 to 6 hours, intravenously or intramuscularly, for mild to moderate infections. The dosage for severe infections is 1 g intravenously every 4 to 6 hours. Peak serum levels after a single intramuscular injection of oxacillin (500 mg) reach 14 to 16 µg/mL.

Cloxacillin and dicloxacillin are analogs of oxacillin. They are acid stable and thus well absorbed after oral ingestion. After an oral dose of 500 mg of cloxacillin, a peak serum level of 8 µg/mL is reached in 30 to 60 minutes. Dicloxacillin produces serum levels that are twice as high as those of cloxacillin. Serum levels of flucloxacillin are similar to those seen with dicloxacillin. The usual oral adult dosage of these penicillins is 500 mg every 6 hours. For dicloxacillin, a dosage of 125 to 250 mg every 6 hours may suffice.

Oxacillin, cloxacillin, and flucloxacillin can be given intramuscularly or intravenously, although dicloxacillin can be given intramuscularly. For mild infections, 250 mg every 6 hours is recommended. For moderate infections, the usual dosage is 1 g every 4 hours, and in severe infections, this is increased to 2 g every 4 hours.

Nafcillin is poorly absorbed and is unreliable when used orally. It can be given either intramuscularly or intravenously. The usual adult dosage is 1 g every 4 hours but can be increased to 2 g every 4 hours for severe infections. After a 1-g intramuscular injection, a peak serum level of 8 µg/mL of nafcillin is reached in about 1 hour. By 6 hours, the level is 0.5 µg/mL.

Side Effects

Methicillin, isoxazolyl penicillins, and nafcillin are contraindicated in penicillin-allergic patients because they can produce any of the hypersensitivity reactions described for penicillin G. Methicillin has been associated with drug fever and leukopenia. In addition, interstitial nephritis may result from the use of large doses of intravenous methicillin. Most patients recover from the methicillin-associated interstitial nephritis after stopping the agent.

The isoxazolyl penicillins may produce nausea and diarrhea with oral administration. Oxacillin may cause fever, nausea, and vomiting in association with abnormal liver function test results. Neutropenia has been noted as well. With very large doses, neurotoxicity occurs, particularly in patients with impaired renal function.

Nafcillin has been reported to cause nephropathy and neutropenia on rare occasion.

Cost

The penicillinase-resistant group of penicillins are more-expensive drugs than penicillin G. They should be used only in the treatment of staphylococcal strains resistant to penicillin G.

Use in Pregnancy

All the penicillinase-resistant penicillins are capable of crossing the placenta. No untoward effects on the fetus have been described.

Metabolism

Methicillin is excreted in urine, both by glomerular filtration and by tubular secretion. Up to 80% of an injected dose can be recovered from urine. A small percentage (2% to 3%) of the administered drug is excreted in bile. The unexcreted methicillin is inactivated in the body by the liver. Methicillin is widely distributed throughout the body.

Isoxazolyl penicillins are mainly excreted in the urine, with dicloxacillin and flucloxacillin present in larger amounts than cloxacillin, of which 30% of an oral dose is excreted in the urine. Oxacillin is excreted in smaller amounts than cloxacillin.

Excretion occurs by glomerular filtration and tubular secretion. These penicillins are also excreted in the bile to a small extent. Inactivation of the isoxazolyl penicillins probably occurs in the liver.

After administration of nafcillin, 30% of the dose can be recovered from the urine. Between 5% and 10% of a dose is excreted in bile. The remainder of the nafcillin is inactivated in the liver. Nafcillin reaches high concentrations in the CSF of patients with normal meninges and in those with inflamed meninges.

Indications in Obstetrics and Gynecology

The penicillinase-resistant penicillins are indicated solely for the treatment of infections due to *S. aureus.* Examples include wound infection, mastitis, endocarditis, osteomyelitis, and toxic shock syndrome.

Aminopenicillins

The aminopenicillins are semisynthetic derivatives of 6-APS and include ampicillin, amoxicillin, and antibiotics structurally related to ampicillin-amoxicillin, such as epicillin, cyclacillin, hetacillin, pivampicillin, talampicillin, bacampicillin, and metampicillin.

Spectrum of Activity

Ampicillin and amoxicillin have identical spectra. They are active against most of the bacteria that are sensitive to penicillin G. However, they are also active against some of the Gram-negative bacteria that are resistant to penicillin G. Like penicillin G, they are bactericidal antibiotics that inhibit cell wall synthesis.

Against aerobic Gram-positive cocci, ampicillin is generally as effective as penicillin G. Thus, group A and group B b-hemolytic streptococci, most *S. pneumoniae,* and the b-hemolytic streptococci of the viridans group are susceptible. Nearly all *S. aureus* organisms are resistant to ampicillin. Unlike penicillin G, ampicillin is effective against enterococcal strains of the group D streptococci. The anaerobic Gram-positive cocci such as *Peptostreptococcus* species are almost always sensitive to ampicillin.

Among Gram-positive aerobic bacilli, *C. diphtheriae, B. anthracis*, and *L. monocytogenes* are generally susceptible to ampicillin. Ampicillin is active against anaerobic Gram-positive spore-forming bacilli such as clostridia and anaerobic Gram-positive non–spore-forming bacilli such as *Actinomyces, Eubacterium, Bifidobacterium, Propionibacterium,* and *Lactobacillus* species.

Unlike penicillin G, ampicillin is effective against some of the Enterobacteriaceae. Although *E. coli* is often sensitive, increasing resistance by this organism has made ampicillin an unreliable choice for therapy. Unless it is a b-lactamase–producing strain, *Proteus mirabilis* is susceptible to ampicillin. *Enterobacter, Klebsiella, Serratia, Citrobacter,* and indole-positive *Proteus* strains are generally resistant to ampicillin. Salmonellae are usually sensitive, but resistant strains have occurred. On the other

hand, *Shigella* species tend to be resistant.

Among the other Gram-negative aerobic bacteria, *P. aeruginosa* is always resistant to ampicillin. *Haemophilus influenzae* type b was generally sensitive to ampicillin, but plasmid-mediated ampicillin resistance has occurred. *N. gonorrhoeae* strains are now less susceptible to ampicillin. Penicillinase-producing *N. gonorrhoeae* (PPNG) strains are completely ampicillin resistant. *N. meningitide*s organisms remain sensitive. Similar to the pattern with penicillin G, many of the *Bacteroides* and *Fusobacterium* species are ampicillin sensitive. The notable exceptions are *B. fragilis* group, *P. bivia,* and *Prevotella disiens.* Mycoplasmas and rickettsiae are ampicillin resistant, chlamydiae are relatively resistant, but *Chlamydia trachomatis* cervicitis may be treated with amoxicillin, which is an alternative treatment in pregnancy (2).

Dosage and Route

The usual oral dosage of ampicillin is 250 to 500 mg every 6 hours. After oral administration of 500 mg, peak serum levels of 3 µg/mL are obtained at approximately 2 hours, and the drug is still detectable at 6 hours. Doubling the dose results in a doubling of the serum level. Oral absorption of ampicillin is significantly lowered if it is taken with meals. For amoxicillin, the usual dosage is 250 mg three times a day.

An intramuscular preparation of ampicillin is available but rarely necessary. The usual dosage is 0.5 to 1.0 g every 6 hours. After a 500-mg injection, a peak serum level of 10 µg/mL is achieved in 1 hour, and levels persist for 4 hours.

The usual intravenous dosage is 1 to 2 g every 4 to 6 hours by intermittent infusion, depending on the severity of the clinical infection.

Amoxicillin is significantly better absorbed than ampicillin when given orally, and peak serum levels are approximately 2 to 2.5 times those achieved with a similar dose of ampicillin. The usual adult dosage of amoxicillin is 250 to 500 mg every 6 to 8 hours.

Bacampicillin, when administered orally, is totally hydrolyzed to free ampicillin. It is absorbed better than ampicillin in the presence of food. Peak serum levels of 1.5 to 2 times greater are achieved with bacampicillin, compared with a similar dose of ampicillin. The usual adult dosage is 200, 400, or 800 mg every 8 to 12 hours.

Side Effects

Ampicillin and the other aminopenicillins may cross-react with other penicillins and should, therefore, not be used in patients with a history of penicillin allergy. Any of the hypersensitivity reactions described for penicillin G may occur with ampicillin. The incidence of rash in ampicillin users is much greater than that reported with use of penicillin G. Five percent to 7% of patients treated with ampicillin develop a diffuse macular rash. However, these rashes are specific for ampicillin and do not represent a true penicillin allergy.

Gastrointestinal side effects such as nausea and diarrhea occur commonly but are generally not serious. Because of their enhanced gastrointestinal absorption, the

aminopenicillins, except ampicillin, are associated with fewer gastrointestinal side effects. More rarely, pseudomembranous colitis has been reported with ampicillin use. Unusual side effects noted in ampicillin treatment include nephropathy, agranulocytosis, and encephalopathy.

Ampicillin may impair the absorption of oral contraceptives and thus can be associated with breakthrough bleeding. *Monilia* vaginitis may develop secondary to ampicillin suppression of the normal vaginal microflora.

Cost

Ampicillin is a relatively inexpensive antibiotic, in both oral and parenteral forms. For oral amoxicillin, the cost is similar. The other aminopenicillins are more costly than ampicillin, and the additional cost may limit their use.

Use in Pregnancy

Ampicillin has been used extensively in pregnancy. No adverse fetal effects have been associated with ampicillin, so the drug is considered safe for use in pregnancy. In pregnant woman, serum levels of ampicillin are approximately 50% of those obtained in nonpregnant women. This is the result of the significant increases in plasma volume and renal clearance of ampicillin that occur in pregnancy.

Ampicillin rapidly crosses the placenta, and after a single maternal dose, peak cord blood levels are 40% of the peak maternal levels. In turn, amniotic fluid levels are lower than those in the umbilical cord.

Experience with the other aminopenicillins in pregnancy is limited to date, and they are not generally recommended for use in pregnant women.

Metabolism

Like penicillin G, ampicillin is largely excreted in urine as the result of glomerular filtration and tubular secretion. After oral administration, 75% of a dose is excreted in the urine. The remainder of an ampicillin dose is either excreted in the bile or inactivated in the liver.

Ampicillin is evenly distributed throughout body tissues, with levels in the kidneys and liver being significantly greater than serum levels. Although only very low levels can be detected in normal CSF, high levels of ampicillin are achieved in the CSF with inflamed meninges.

Indications in Obstetrics and Gynecology

Ampicillin is widely used in the therapy for asymptomatic bacteriuria, acute cystitis, and acute pyelonephritis in pregnant and nonpregnant women. Because of increasing resistance of *E. coli,* ampicillin should not be used by itself in the empiric treatment of urinary tract infection (UTI), particularly pyelonephritis.

Although in the past ampicillin alone or in combination with an aminoglycoside was

commonly used for the treatment of mixed aerobic-anaerobic soft tissue pelvic infections such as endomyometritis, pelvic cellulitis, or pelvic inflammatory disease (PID), the recognition of the need to provide therapy against Gram-negative anaerobes in such infections has resulted in a significant decrease in the use of ampicillin on obstetric and gynecologic services.

Ampicillin and penicillin are the drugs of choice for group B streptococci and are included in the treatment of intraamniotic infection (chorioamnionitis) in combination with agents effective against anaerobes and Gram-negative aerobes. Ampicillin is also the optimal drug for the treatment of *L. monocytogenes* infections. Ampicillin is an alternative to penicillin G in intrapartum prophylaxis of perinatal group B streptococcal infections (4).

Finally, ampicillin has been used effectively as a prophylactic antibiotic with cesarean sections and vaginal hysterectomy. Because the other aminopenicillins have an antibacterial spectrum similar to that of ampicillin, the indications for their use are similar to those for ampicillin. Because of enhanced oral absorption, amoxicillin has replaced oral ampicillin in the treatment of UTIs.

Antipseudomonal Penicillins

The antipseudomonal group of penicillins include the carboxypenicillins—carbenicillin and ticarcillin—and the ureidopenicillin azlocillin. The major importance of these antimicrobial agents is their activity against *Pseudomonas.* However, they are all susceptible to b-lactamase enzymes produced by Gram-negative and Gram-positive organisms.

Spectrum of Activity

The spectrum of activity of carbenicillin is similar to that of ampicillin. However, it does possess activity against *P. aeruginosa* and certain indole-positive *Proteus* species. Carbenicillin is less active than ampicillin against the facultative streptococci, although its activity against *N. gonorrhoeae, N. meningitides,* and *Haemophilus* is similar to that of ampicillin. *Klebsiella pneumoniae* is resistant. At high concentrations, carbenicillin is also active against anaerobic bacteria including *B. fragilis,* although not to the extent of clindamycin, chloramphenicol, metronidazole, or cefoxitin. Carbenicillin acts synergistically with aminoglycosides to inhibit *P. aeruginosa.* This is clinically important because resistance to carbenicillin often develops among *P. aeruginosa* during therapy. The antibacterial spectrum of ticarcillin is similar to that of carbenicillin with the exception that it is two to four times more active against *P. aeruginosa.* However, strains of *P. aeruginosa* that are highly resistant to carbenicillin are also resistant to ticarcillin. Azlocillin is a ureidopenicillin whose main advantage is its significantly enhanced activity against *P. aeruginosa,* compared with that of carbenicillin or ticarcillin. All three of these agents are ineffective against b-lactamase–producing *S. aureus*.

Dosage and Route

Carbenicillin is not absorbed after oral administration and is available in intramuscular or intravenous forms. An oral form, carbenicillin indanyl sodium, is available but is useful only for UTIs because adequate serum concentrations are not

achieved. For the treatment of systemic *Pseudomonas* infections or anaerobic infection, intravenous intermittent doses of carbenicillin (5 g every 3 to 4 hours) are required (total 30 to 40 g daily). Parenteral carbenicillin for *Pseudomonas* UTIs requires 1 to 2 g every 4 to 6 hours. The usual adult dosage for oral carbenicillin (provided as carbenicillin indanyl sodium) is 0.5 to 1.0 g every 6 hours.

After an intramuscular dose of 1 g, peak carbenicillin serum levels of 20 µg/mL are achieved in 1 hour, and no drug is detectable by 4 hours. Although these serum levels are inadequate for *Pseudomonas* or anaerobic infections in soft tissue, the urine levels reach 2,000 to 4,000 µg/mL, which are sufficient for the treatment of *Pseudomonas* UTI. With an intravenous infusion of 70 to 100 mg of carbenicillin per kilogram of body weight, serum levels of 150 to 200 µg/mL can be obtained; these levels are sufficient, in many instances, for the treatment of soft tissue *Pseudomonas* or anaerobic infections.

With ticarcillin, an adult dosage of 18 to 24 g per 24 hours is recommended for systemic *Pseudomonas* infections or anaerobic infections; this is given as a 3-g dose every 3 to 4 hours. For treatment of UTIs, a dosage of 1 g every 6 hours is recommended. After a 1-g dose of ticarcillin intramuscularly, a mean peak serum level of 35 µg/mL is achieved in 1 hour, and by 6 hours, it is 6 µg/mL. After a 3-g intravenous infusion, mean serum levels postinfusion are 239 µg/mL, and at 4 hours, they are 94 µg/mL.

Azlocillin is administered intravenously in a dosage of 12 to 16 g per day divided into four doses. Administration of a 2-g dose of azlocillin results in peak serum levels of 60 µg/mL at 1 hour.

Side Effects

Carbenicillin, ticarcillin, and azlocillin may provoke any of the hypersensitivity reactions that occur with penicillin G. High doses of carbenicillin may result in neurotoxicity. Each gram of carbenicillin contains 4.7 mEq of sodium. With the use of the required large dosage of 30 to 40 g per day, the potential for sodium overload may occur in patients with cardiac or renal disease. In addition, hypokalemia may occur as a result of this sodium overload. Finally, carbenicillin rarely is associated with bleeding as the result of diminished platelet adhesiveness.

In high doses, ticarcillin also may result in neurotoxicity, electrolyte disturbances similar to those described with carbenicillin, and altered platelet function. The lower required dose of ticarcillin (compared with that of carbenicillin) is associated with a lower sodium load and less platelet dysfunction.

Cost

The antipseudomonal penicillins are costly antimicrobial agents because of the large doses required.

Use in Pregnancy

Carbenicillin, ticarcillin, and azlocillin have not been used extensively during pregnancy. Like other penicillins, they are most likely safe to use during pregnancy.

However, they should be used in pregnant women only when no safe alternative is available.

Metabolism

Carbenicillin is excreted via the kidney, with about 95% of a parenteral dose excreted into the urine during the first 6 hours after administration. It is excreted via glomerular filtration and tubular secretion. A small amount (less than 1%) of carbenicillin is excreted in the bile or inactivated in the liver. Similarly, ticarcillin and azlocillin are also primarily excreted via the kidneys.

Indications in Obstetrics and Gynecology

The clinical role for carbenicillin and ticarcillin in obstetrics and gynecology is now very limited. Although clinical studies have demonstrated relatively good efficacy with these agents (as single agents or in combination with aminoglycosides) in the treatment of mixed aerobic-anaerobic soft tissue infections of the pelvis (5,6), the introduction of the ureidopenicillins, mezlocillin and piperacillin, into clinical practice has significantly reduced their usefulness.

Although *Pseudomonas* infections of soft tissue are rare on obstetric and gynecologic services, when these infections do occur, azlocillin is an appropriate therapeutic agent. Its major advantage over aminoglycosides is a decreased potential for nephrotoxicity or ototoxicity. For serious *Pseudomonas* infection, azlocillin should be combined with an aminoglycoside.

Extended-Spectrum Penicillins

The new ureidopenicillins, such as mezlocillin (Mezlin) and piperacillin (Pipracil), have replaced the carboxypenicillins (carbenicillin and ticarcillin). Compared with carbenicillin and ticarcillin, the ureidopenicillins have extended coverage against the Enterobacteriaceae, a diminished sodium load, and increased bioavailability in CSF, amniotic fluid, and cord blood. In addition, they provide increased activity against many aerobic and anaerobic Gram-positive cocci, including enterococci.

Spectrum of Activity

Mezlocillin is fairly similar to carbenicillin and ticarcillin in its antibacterial spectrum, with several important differences. It is more active against *Proteus* and *Enterobacter* strains. Mezlocillin is significantly more active than carbenicillin or ticarcillin against *K. pneumoniae,* with nearly 75% of *Klebsiella* species being susceptible. Mezlocillin is more active against enterococci and somewhat more active against *B. fragilis*; however, most *S. aureus* strains are resistant.

Piperacillin demonstrates a wide spectrum of antibacterial activity (8). It is active against most clinically important Gram-negative facultative bacteria, particularly indole-positive *Proteus* species, *Klebsiella,* many *Serratia marcescens,* and *P. aeruginosa*; *E. coli, P. mirabilis, Enterobacter, Citrobacter, Salmonella,* and *Shigella* species are sensitive to low concentrations of piperacillin. Piperacillin demonstrates activity against Gram-positive aerobic bacteria, including the enterococcus. In addition, virtually all clinically important anaerobes, including *B. fragilis* and *P. bivia,*

are sensitive to piperacillin.

The major defect in the spectrum of these agents is lack of coverage for *S. aureus,* 10% of *E. coli,* and some *Klebsiella* species (particularly with piperacillin, which covers only half of *Klebsiella* strains).

Dosage and Route

Mezlocillin (Mezlin) may be administered intramuscularly or intravenously (preferred). The recommended adult dosage is 200 to 300 mg/kg per day, usually given as 3 g intravenously every 4 hours (18 g per day). Up to 24 g per day may be given for severe infections. A 30-minute infusion of 3 g of mezlocillin results in peak serum concentrations of about 260 µg/mL, and by 1 hour and 4 hours, the serum levels are 57 µg/mL and 4.4 µg/mL, respectively.

Piperacillin (Pipracil) is available for intramuscular or intravenous (preferred) administration. The usual adult dosage is 3 to 4 g every 4 to 6 hours as an intravenous infusion (total, 12 to 18 g per day). After a 30-minute intravenous infusion of 4 g of piperacillin, peak serum levels of 215 µg/mL are reached; by 1 hour, the level is 105 µg/mL, and it falls to 15 µg/mL by 4 hours.

Side Effects

As with other penicillins, mezlocillin and piperacillin have been associated with hypersensitivity reactions, nausea, diarrhea, CNS irritability with large doses, and local reactions such as phlebitis.

A major advantage of mezlocillin and piperacillin over carbenicillin and ticarcillin is a significant decrease in sodium load. The ureidopenicillins contain 1.85 mEq/g of sodium, compared with 5.23 mEq/g for carbenicillin and 5.20 mEq/g for ticarcillin. This dramatically reduces the risk of congestive heart failure in patients with cardiovascular compromise.

Cost

Both mezlocillin and piperacillin are expensive antimicrobial agents because of the need for large doses, frequent intravenous administration, and a moderately expensive per-gram cost.

Use in Pregnancy

Because of altered protein binding, the ureidopenicillins can enter cord blood and amniotic fluid in therapeutic concentrations. Experience with these agents in pregnancy is very limited. Being penicillins, they are probably safe for use during pregnancy, but long-term follow-up studies are unavailable.

Metabolism

Like other penicillins, both mezlocillin and piperacillin are primarily excreted by the kidneys. Approximately 55% of a mezlocillin dose appears in urine within 6 hours,

and 26% is excreted in the bile. For piperacillin, nearly 80% of a dose is excreted in urine within 24 hours. Excretion also occurs via the biliary route for piperacillin. Both mezlocillin and piperacillin are widely distributed throughout body tissues. Although little of either drug penetrates the CSF in normal patients, mezlocillin and piperacillin both achieve satisfactory levels in the CSF with inflamed meninges.

Indications in Obstetrics and Gynecology

The *in vitro* studies reviewed previously suggested that mezlocillin or piperacillin might be effective single agents for the treatment of mixed aerobic-anaerobic soft tissue infection in the female pelvis. Clinical investigations have confirmed the efficacy of these agents in the treatment of such infections with clinical cure rates usually, but not always, similar to those achieved using standard regimens such as clindamycin plus gentamicin. These results suggest mezlocillin and piperacillin can be used as reasonable single-agent therapy for many polymicrobial infections in obstetrics and gynecology. Yet, they have not been evaluated as thoroughly as other regimens (e.g., clindamycin-gentamicin, and cefoxitin, or cefotetan).

Both these agents have been used as prophylactic antibiotics in patients undergoing cesarean section or hysterectomy. The coverage of enterococci and *P. aeruginosa* is a theoretic advantage for mezlocillin or piperacillin over commonly used cephalosporins or ampicillin in prophylactic attempts. However, they are significantly more costly than older drugs, and no studies have demonstrated that these agents are better than ampicillin or first-generation cephalosporins for prophylaxis.

Amidino Penicillins

Mecillinam, although derived from the penicillin nucleus, 6-APS, is actually in a new class of penicillins. Pivmecillinam, an ester of mecillinam, is the preparation for oral administration.

Spectrum of Activity

Mecillinam differs from most penicillins in its spectrum of activity. Unlike other penicillins, mecillinam has poor activity against Gram-positive bacteria and is much more active against Gram-negative organisms. Thus, it is highly active against most Enterobacteriaceae including *E. coli, Klebsiella, Enterobacter, P. mirabilis, Proteus vulgaris,* and *Citrobacter.* Most *S. marcescens* are resistant, as are almost all *P. aeruginosa* and *B. fragilis.* Both *N. gonorrhoeae* and *H. influenzae* are significantly less susceptible to mecillinam than to ampicillin. Interestingly, mecillinam acts synergistically with other b-lactam antibiotics—penicillins and cephalosporins—against most Enterobacteriaceae.

Dosage and Route

Mecillinam is administered intramuscularly or intravenously. The dosage is 200 to 400 mg every 6 hours but can be increased to 600 mg. The peak serum level after a 200-mg intravenous dose is 6.5 µg/mL, which falls to 2 µg/mL by 1 hour.

Pivmecillinam is usually administered in 400-mg doses every 6 hours, orally. Mean peak serum levels of 2.5 µg/mL are achieved 1.5 hours after administration of a

400-mg dose.

Side Effects

Mecillinam use is associated with few toxic effects. Gastrointestinal side effects are uncommon, as are the penicillin-type hypersensitivity reactions.

Use in Pregnancy

The use of mecillinam in pregnancy is not clear. Animal studies suggest that it achieves low levels in the fetus.

Metabolism

Mecillinam is excreted in the urine; 60% of parenterally administered and 40% of orally administered drug appear in the urine within 24 hours. The drug is also excreted in bile, where levels higher than those in serum are obtained.

Indications in Obstetrics and Gynecology

Little available information on the use of mecillinam in obstetrics and gynecology exists. Its major appeal would be as a safe b-lactam agent in the treatment of infections due to Enterobacteriaceae (e.g., pyelonephritis) as a single agent or in combination with drugs effective against Gram-positive aerobes and anaerobic bacteria in mixed infections. The final answer must await such clinical trials.

Penicillin-b-Lactamase-Inhibitor Combinations

A new approach to developing new antimicrobial agents that are resistant to degradation by b-lactamase enzymes involves developing compounds that inhibit these enzymes and combining them with older b-lactam antibiotics. This results in an enhanced spectrum of activity against a wide variety of aerobic and anaerobic bacteria. Three enzyme inhibitors, clavulanic acid, sulbactam, and tazobactam, have been developed, and their combination with penicillins has led to the introduction of clinically available agents: amoxicillin–clavulanic acid (Augmentin), ticarcillin–clavulanic acid (Timentin), sulbactam-ampicillin (Unasyn), and piperacillin-tazobactam (Zosyn).

Amoxicillin–Clavulanic Acid (Augmentin)

The addition of clavulanic acid, a suicide inhibitor of b-lactamases, to amoxicillin has resulted in an antimicrobial agent (Augmentin) that has a markedly increased spectrum of activity against a wide variety of aerobic and anaerobic bacteria. Augmentin has demonstrated success in the treatment of skin infections due to b-lactamase–producing *S. aureus,* otitis media due to *H. influenzae,* UTIs due to b-lactamase–producing *E. coli* and *Klebsiella,* and PPNG.

However, it is available only as an oral agent. Theoretically, Augmentin plus doxycycline is an excellent ambulatory regimen for PID. However, attempts to use Augmentin plus doxycycline for the treatment of PID have been limited by a high

incidence of nausea and vomiting (9). Thus, Augmentin has a limited role in the treatment of pelvic infections.

Ticarcillin–Clavulanic Acid (Timentin)

Timentin is the combination of ticarcillin (3g) and clavulanic acid (100 mg). The addition of clavulanic acid, a b-lactamase inhibitor, to ticarcillin resulted in a combination compound that has markedly enhanced activity. Compared with ticarcillin alone, Timentin has increased activity against *S. aureus, E. coli, Klebsiella, B. fragilis,* other b-lactamase–producing *Bacteroides,* and *N. gonorrhoeae,* including PPNG (10). Timentin has demonstrated excellent *in vitro* activity against the *B. fragilis* group of organisms, which was equivalent to that of imipenem (11). However, enterococci and MRSA remain relatively resistant.

The pharmacology of ticarcillin is not significantly altered by the addition of clavulanic acid and thus is similar to that discussed already. Both drugs have a serum half-life of about 1 hour after intravenous infusion. Sixty percent to 90% of ticarcillin and 35% to 45% of clavulanic acid are excreted unchanged in the urine. Renal insufficiency leads to accumulation, so dosage adjustment is necessary for patients with renal impairment. After intravenous infusion, both ticarcillin and clavulanic acid are widely distributed, with peak serum levels of 400 µg/mL for ticarcillin and 11 µg/mL for clavulanic acid. The dosage of Timentin (3 g of ticarcillin and 100 mg of clavulanic acid) is every 4 to 6 hours, depending on the severity of infection. This combination can inactivate aminoglycosides and should not be infused at the same time as an aminoglycoside.

Side effects are rare and usually mild. Among the most common are phlebitis, rash, diarrhea, mild elevations in liver function test results, and rarely, hematologic abnormalities such as eosinophilia, leukopenia, thrombocytopenia, or anemia.

The cost per day for Timentin (3.1 g every 6 hours) is high. In comparative studies (12,13), Timentin was found to be as effective as clindamycin-gentamicin. These results make Timentin a reasonable choice for many polymicrobial infections, but there has been more variability in cure rate than is seen with comparable regimens.

Ampicillin-Sulbactam (Unasyn)

The addition of sulbactam to ampicillin significantly extended the antibacterial spectrum of ampicillin to include b-lactamase–producing strains of *H. influenzae, N. gonorrhoeae,* many anaerobes (including *B. fragilis, B. bivius,* and *B. disiens*), *E. coli, Klebsiella, Enterobacter aerogenes, S. aureus,* and *S. epidermidis.* However, ampicillin-sulbactam is not active against *P. aeruginosa, Enterobacter cloacae,* or *Serratia* species.

Administration of ampicillin and sulbactam together has no effect on the pharmacokinetics of these agents. The serum half-life for both drugs is approximately 1 hour. After intravenous infusion, ampicillin and sulbactam are widely distributed, and after 500 mg infusion of each agent, serum levels rapidly peak at about 30 µg/mL for ampicillin and 43 µg/mL for sulbactam. Eighty-five percent of both drugs are excreted in urine within 24 hours. Small amounts of both drugs appear in breast milk (10). Ampicillin-sulbactam is available as 1 g of sulbactam to

every 2 g of ampicillin. The usual dosage is 0.5 to 1 g of sulbactam plus 1 to 2 g of ampicillin every 6 hours. As with ampicillin itself, the kinetics of ampicillin-sulbactam is altered in pregnancy. There is more rapid elimination and a shorter serum half-life (14).

The most common side effects have generally been nausea, vomiting, diarrhea, or allergic reactions. Minor elevations in liver function test results have been infrequently reported.

In clinical studies, ampicillin-sulbactam has been demonstrated to be effective in the treatment of soft tissue pelvic infections including endometritis and PID. However, ampicillin-sulbactam is not recommended as a treatment of PID by itself (2,17). In a large study, equivalent response rates were also found by McGregor et al. (17). For endometritis, the good response rate was 89% (141 of 159) for ampicillin-sulbactam versus 91% (139 of 153; *p* values were not significant [NS]) for clindamycin-gentamicin; for PID, the good response rate was 86% (47 of 55) in the ampicillin-sulbactam group versus 90% (43 of 48; *p* = NS) in the cefoxitin-doxycycline group (17).

The cost per day for 3 g every 6 hours is moderately high but may be less than that of other new antibiotics.

Based on the efficacy in clinical trials and the moderate cost, ampicillin-sulbactam is also a reasonable choice for treatment of polymicrobial infections. Among the penicillin b-lactamase combinations, it is the most widely studied.

Piperacillin-Tazobactam (Zosyn)

Another combination is piperacillin-tazobactam (Zosyn). Tazobactam is also an irreversible b-lactamase inhibitor. *In vivo,* this combination also shows enhanced activity compared with the penicillin alone. In a large multicenter comparative trial, Sweet et al. (18) compared Zosyn (3 g of piperacillin and 375 mg of tazobactam) with clindamycin-gentamicin in various pelvic infections (50% endometritis, 39% PID, 11% other gynecologic infections) and reported the following favorable response rates: 85% (166 of 196) for Zosyn and 87% (90 of 103) for clindamycin-gentamicin; *p* = NS). In this trial, diarrhea occurred more commonly in the piperacillin group (9.7% vs. 2.9%; *p* = 0.04), although most cases were mild to moderate and generally did not require therapy. In noncomparative trials, this antibiotic also led to high response rates (19).

CEPHALOSPORINS

Many of the new antibiotics introduced over the past 15 to 20 years have been cephalosporins. Not surprisingly, these agents are very commonly prescribed antibiotics. Cephalosporins are classified according to their chemical structure, differences in pharmacology, b-lactamase resistance, and spectrum of activity. The most commonly used classification system is by generations according to antimicrobial activity (Table 23.5). Since the introduction of the first cephalosporin in 1964, there has been a virtual explosion of the cephalosporins and 21 are currently available in the United States (1). Three generations of cephalosporins have been marketed. In addition, cefepime has been classified as a fourth-generation

cephalosporin by some authorities because of its unique extended spectrum of activity (1).

TABLE 23.5. CLASSIFICATION OF CEPHALOSPORINS

First-Generation Cephalosporins

The cephalosporin antibiotics make up an extensive group, all of which are comprised of a 7-aminocephalosporanic acid with a d-aminodipic acid side chain. Changes in the side chain of this molecule have led to the development of cephalothin (Keflin), cefazolin (Kefzol, Ancef), cephapirin (Cefadyl), cephalexin (Keflex), and other so-called first-generation cephalosporins. Because of similar properties, these antibiotics are discussed as a group (2,3 and 4). Currently, only cefazolin, cephalexin, and cefadroxil are marketed in the United States.

Spectrum of Activity

The first-generation cephalosporins are primarily active against many aerobic Gram-positive cocci (including *S. aureus,* but excluding the enterococcus). They possess moderate activity against *N. gonorrhoeae* (exclusive of PPNG strains) and some aerobic Gram-negative rods, including community-acquired *E. coli, P. mirabilis* (indole negative), *K. pneumoniae,* and *Moraxella catarrhalis.* Resistant aerobic Gram-negative organisms include *Enterobacter, Pseudomonas,* and *Serratia* species. First-generation cephalosporins have poor activity against *H. influenzae,* methicillin-resistant staphylococci (despite *in vitro* sensitivity), and penicillin-resistant pneumococci. Although some anaerobes are susceptible to cephalosporins, other antibiotics are preferable because of their broader activity, particularly against the *Bacteroides* and *Prevotella* group of bacteria, which produce b-lactamase enzymes. *C. trachomatis*and the genital mycoplasmas are resistant.

The mechanism of action of cephalosporin antibiotics is quantitatively and qualitatively similar to that of penicillin. Cephalosporins interfere with cell wall synthesis. In particular, cephalosporins interfere with the biosynthesis of peptidoglycan in the cell wall by binding to and inactivating penicillin-binding proteins

(1).

As reviewed by Asbel and Levison (1), there are three mechanisms of microbial resistance to the cephalosporins: (a) alteration and decreased affinity of penicillin-binding proteins; (b) production of b-lactamases that inactivate the agent; and (c) changes in the bacterial outer cell wall (loss of porin channels) that limit the ability of the drug to reach the penicillin-binding proteins.

Dosage and Route

Two first-generation cephalosporin antibiotics, cephalexin (Keflex) and cefadroxil (Duricef) are absorbed orally. Cephalexin reaches maximum serum concentrations of 15 to 18 µg/mL within 1 hour after a 500-mg oral dose and has a half-life of 0.9 hours. Cefadroxil has a half-life of 1.2 hours and reaches a peak serum concentration of 16 µg/mL. For adults, the usual dosage is 250 mg every 6 hours for cephalexin and 1 g twice daily for cefadroxil. Oral cephalosporins are very well absorbed from the gastrointestinal tract.

When parenteral cephalosporins are administered by either the intramuscular or the intravenous route, they are readily absorbed and widely distributed. Cephalosporins are detectable in ascitic, synovial, and pericardial fluids.

Cefazolin (Ancef, Kefzol) may be administered by the intramuscular or intravenous route. After a 1-g intravenous infusion, cefazolin reaches a peak serum concentration of 80 µg/mL. The half-life of cefazolin is 1.8 hours, so adult dosing ranges from 0.5 to 1.5 g every 6 to 8 hours (the usual adult dosage is 1 g every 8 hours).

Because excretion of most cephalosporins is delayed in patients with diminished renal function, the dose should be decreased modestly for these persons. The first-generation cephalosporins have similar antibacterial spectra. Although slight differences may be observed in the activity of these antibiotics against particular strains, these differences appear not to be clinically significant. Although cefazolin achieves serum concentrations that are significantly higher than those of the other cephalosporins, all these compounds achieve concentrations adequate to inhibit most cephalosporin-susceptible bacteria.

Side Effects

The cephalosporins are generally very well tolerated. Fever, eosinophilia, serum sickness, and rashes occur rarely, and transient neutropenia has been observed. Although Coombs positivity is commonly observed in patients receiving cephalosporins, particularly cephalothin, hemolytic anemia is extremely uncommon.

Pain on intramuscular injection is uncommon with cefazolin. Phlebitis has been observed with intravenous administration of all the cephalosporins. Nephrotoxicity has been very rarely observed after administration of current cephalosporins.

Cross-reactivity may exist between penicillins and cephalosporins (5). Although precise incidence data are not available, persons who have had an immediate hypersensitivity reaction to penicillin, manifested by urticaria, wheezing, or anaphylaxis, are at greater risk for the development of similar reactions after

cephalosporin administration. Cephalosporins are contraindicated in such individuals.

Cost

Costs of the first-generation cephalosporins have come down in the last few years. For oral preparations, the cost per day for cephalexin (500 mg orally four times a day) is approximately $1, but other preparations may be more expensive. For injectable preparations, the cost per day for cefazolin (1 g every 8 hours) is approximately $4.

Use in Pregnancy

Cephalosporins cross the placenta rapidly after intravenous injection to the mother and achieve adequate levels in cord blood and amniotic fluids. To date, no adverse fetal effects have been reported for this group of antibiotics.

Metabolism

Cefazolin is excreted by the renal route. The primary mode of excretion is tubular excretion, and excretion is delayed in the presence of diminished renal function. Approximately 80% of cefazolin is bound to protein.

Indications in Obstetrics and Gynecology

The cephalosporins have gained an important role in the practice of medicine; they are among the most commonly used group of antibiotics in hospitals in this country. In other specialties, they have been frequently used as prophylactic agents in cardiac, orthopedic, vascular, and gastrointestinal surgery. They are also active and effective agents in the treatment of staphylococcal and a limited number of Gram-negative infections.

Yet, there are no situations in which they are clearly the drugs of choice for therapy. In most situations, other antibiotics are clearly preferable. Thus, for a penicillin-sensitive organism, penicillin should be used, and for treating infections caused by *S. aureus,* a penicillinase-resistant penicillin should be used.

In a number of situations, however, the first-generation cephalosporin antibiotics are valuable. The first of these is in the patient with delayed-type penicillin hypersensitivity. A cephalosporin may be used safely in most of these patients in place of penicillin, ampicillin, or methicillin, oxacillin, cloxacillin, and nafcillin. The second situation for using a cephalosporin antibiotic may be in treating some UTIs. Depending on the susceptibility pattern of the causative microorganism, a first-generation cephalosporin may be a good choice for the empiric treatment of pyelonephritis in pregnancy. With rising resistance of bacteria to ampicillin, cephalosporins may offer a high degree of both efficacy and safety. In patients with severe pyelonephritis and shock or with multiple previous infections, a broader spectrum of therapy is indicated. Finally, a cephalosporin may be used in the initial treatment (with or without an aminoglycoside) of *postoperative* (or other hospital-acquired) pneumonia, because it may be caused by either Gram-positive

cocci or Gram-negative aerobes, particularly *Klebsiella* species.

First-generation cephalosporins have been studied widely for prophylaxis and are now considered the drugs of choice by many experts for prophylaxis in obstetric and gynecologic procedures (Chapter 24, Antibiotic Prophylaxis in Obstetrics and Gynecology).

Second-Generation Cephalosporins

As noted by Karchmer (6), the second-generation cephalosporins actually contain two distinct groups: the true cephalosporins and the cephamycins. The former group includes cefamandole (Mandol), cefaclor (Ceclor), cefonicid (Monocid), cefprozil (Cefzil), cefuroxime (Zinacef), cefuroxime axetil (Ceftin), and loracarbef (Lorabid), whereas cefoxitin (Mefoxin) and cefotetan (Cefotan) are in the latter group (Table 23.5). Cefoxitin (Mefoxin) and cefamandole (Mandol) became available in late 1978. Both have an extended spectrum of activity compared with previous cephalosporins. As a result of this expanded spectrum of activity, particularly against anaerobes by cefoxitin, effective single-agent antimicrobial therapy for polymicrobic intraabdominal and pelvic infections became available and revolutionized the approach to treatment of these mixed aerobic-anaerobic infections. Most of these second-generation cephalosporins are not commonly used in pelvic infections. More recently, additional cephalosporins that belong to this group have been introduced. Thus, among the second-generation drugs, only cefoxitin and cefotetan are discussed in detail.

Spectrum of Activity (7,8)

Like the penicillins and other cephalosporins, the second-generation cephalosporins are bactericidal, inhibiting cell wall synthesis. The true cephalosporins among the second-generation agents have significantly improved activity against *H. influenzae, M. catarrhalis, N. meningitidis,* and *N. gonorrhoeae* compared with first-generation drugs (6). They provide comparable to improved activity against staphylococci and nonenterococcal streptococci. In addition, they have enhanced activity against some Enterobacteriaceae (6). The cephamycins provide significantly enhanced activity against anaerobic bacteria, particularly the *B. fragilis* group, *Bacteroides* species, *Prevotella* species, and *Porphymonas* species, compared with first-generation cephalosporins and the true cephalosporins among the second-generation cephalosporins. Cefotetan, in particular, has enhanced activity against many Enterobacteriaceae: Cefoxitin and cefotetan have good activity against *Neisseria* species but decreased activity against staphylococci, compared with first-generation cephalosporins or the true cephalosporins among the second-generation cephalosporins (6). In addition, *Pseudomonas* species are highly resistant to all of these new agents. *N. gonorrhoeae,* including penicillinase-producing strains, is susceptible to cefoxitin and cefotetan. Gram-positive anaerobic organisms are susceptible to these agents and to penicillin and older cephalosporin antibiotics.

Against Gram-negative anaerobes, cefoxitin and cefotetan clearly have better activity than older cephalosporins. Cuchural et al. (8) reported that surveillance of roughly 1,200 isolates of the *B. fragilis* group showed only 5% resistance to cefoxitin during 1984 and 1985. More recently, Wexler et al. (10) have shown that cefoxitin has maintained good activity against *B. fragilis* species (90% susceptible at 32 µg/mL, 99% susceptible at 64 µg/mL) and excellent activity against most other anaerobes (90% susceptible at 16 µg/mL or less). Cefamandole is *not* as active against the *B.*

fragilis group as cefoxitin. *In vitro* susceptibility testing has demonstrated that the MIC_{50} (minimum inhibitory concentration) for *P. bivia* and *P. disiens* is twofold to fourfold higher for cefotetan than cefoxitin. However, clinical studies have demonstrated equal efficacy in the treatment of obstetric and gynecologic infections (see the "Indications in Obstetrics and Gynecology" section). Susceptible organisms have MIC values of less than 16 µg/mL; intermediate organisms have MIC values of 32 µg/mL.

The antimicrobial spectra of cefonicid, ceforanide, and cefuroxime are very similar to that of cefamandole (11). These agents are not active against the *B. fragilis* group of organisms or other b-lactamase–producing *Bacteroides* such as *B. bivius, B. disiens,* or the pigmented *Bacteroides.* Thus, their use in obstetrics and gynecology is limited. Cefaclor is an oral agent that is more active against Gram-negative bacilli than the oral first-generation cephalosporin cephalexin. As with older cephalosporins, *C. trachomatis* and the genital mycoplasmas are resistant to the second-generation cephalosporins.

Dosage and Route

Cefoxitin, cefotetan, and cefamandole are administered parenterally. For initial treatment of most infections with cefoxitin, the dosage is 1 to 2 g every 6 hours intravenously. With cefotetan, the dosage is 1 to 2 g every 8 to 12 hours. For cefamandole, the comparable dosage is 2 to 3 g every 6 hours. At the lower range of these dosages, these agents can be given intramuscularly.

Because these agents are excreted mainly in the urine, the dose should be reduced somewhat in patients with renal impairment. For example, the dosage for a patient with moderate renal failure (those with a creatinine clearance of 10 to 50 mL per minute) should be reduced to 1 g every 8 to 12 hours, and for a patient with severe renal failure (creatinine clearance of less than 10 mL per minute, 1 g every 24 hours.

After a 1-g intravenous injection of either drug, peak levels average approximately 100 µg/mL in 0.5 hours, and concentrations fall to 1 µg/mL in about 3 to 4 hours. Cefotetan has a longer half-life.

Cefuroxime has a longer serum half-life than cefamandole (1.5 vs. 0.5 hours) and can be dosed every 8 hours. The serum half-life of ceforanide is 3 hours, and it is administered every 12 hours. Cefonicid has a long serum half-life of 4.5 hours, and one dose a day has been effective for infections due to susceptible organisms (12).

Side Effects

These drugs, like other cephalosporins, are generally well tolerated. (Please see previous discussion for comments on hypersensitivity, renal, liver, and hematologic effects of the cephalosporins.) One of the problems with some antibiotics in this class is local irritation on intramuscular or intravenous injection. In clinical trials, pain on intramuscular injection and thrombophlebitis on intravenous injection were reported infrequently (approximately 5% to 6% of cases) with cefamandole. Pain on intramuscular injection is more common with cefoxitin, although it can be decreased by diluting the drug with 0.5% lidocaine solution.

Cefamandole and cefotetan contain a methyltetrazolethiol (MTT) side chain that inhibits the conversion of inactive to active prothrombin. Thus, these drugs have been associated, on occasion, with hypoprothrombinemia and bleeding (13). Cefoxitin has been associated infrequently with pseudomembranous colitis.

Cost

These agents are relatively expensive and are considerably more costly per gram than the older first-generation cephalosporins. Because of competition between cefoxitin and cefotetan, costs of these drugs have been lowered. In most settings, the cost per day is lower for cefotetan because of its twice-daily dosing schedule, versus four times daily for cefoxitin.

Use in Pregnancy and Placental Transfer

Giamarellou et al. (14) studied the pharmacokinetics of cefoxitin in patients undergoing mid-trimester abortion. They noted that 1 hour after a 2-g intravenous infusion, mean maternal serum levels averaged 30 µg/mL, and by 6 hours after the infusion, the levels had fallen to 0.6 µg/mL. These levels were similar to those noted in nonpregnant women. Amniotic fluid levels of cefoxitin were 2 to 6 µg/mL between 1 and 5 hours after infusion. Cefoxitin, cefotetan, and cefamandole have been widely used in pregnancy and the puerperium and are considered safe for use in pregnancy.

Metabolism

As with other cephalosporins, these antibiotics are excreted mainly by the kidney. Approximately 75% of an intravenous dose can be recovered in the urine within 8 hours. Probenecid inhibits tubular secretion and results in higher blood levels.

Indications in Obstetrics and Gynecology

The extended activity of cefoxitin to include 95% of *B. fragilis* group isolates has made it an attractive single-agent therapy for obstetrics and gynecologic infections. In the late 1980s, cefoxitin emerged as the most commonly used single-agent antimicrobial used for the treatment of pelvic infections. In 1979, Sweet and Ledger (15) evaluated use of 2 g every 8 hours in 109 patients with genital infections. The overall cure rate was 92% (100 of 109). Included were seven patients with pelvic abscess, only three of whom were cured. For salpingitis, endomyometritis, and pelvic abscess, cure rates were 97%, 92%, and 89%, respectively. In a similar report, Ledger and Smith (16) noted a 94% cure rate in 178 patients treated with cefoxitin for various genital tract infections.

However, cefoxitin has not led to high cure rates in other studies. Duff and Keiser (17) compared cefoxitin (2 g intravenously every 8 hours) with penicillin-gentamicin. For cefoxitin, the cure rate was only 61% (19 of 31), and for penicillin-gentamicin, it was 63% (27 of 43). In this study, the authors used a lower dose of cefoxitin, encountered a large number of abscesses, and decided on success or failure of therapy at 48 hours. An intermediate cure rate was reported by Hager and McDaniel (18), who treated 25 cases of pelvic infection with cefoxitin (2 g intravenously every 6

hours). The response rate was 84% (21 of 25). Of the four failures, three required surgical drainage and the fourth showed a response to clindamycin-gentamicin. Larsen et al. (19) reported that cefoxitin was as effective as the clindamycin-gentamicin combination in the treatment of pelvic infections; 37 (90%) of 41 patients treated with cefoxitin and 42 (84%) of 50 patients treated with clindamycin-gentamicin were considered clinical cures.

In several studies, cefotetan has been demonstrated to have clinical efficacy equivalent to that of cefoxitin for the treatment of obstetric and gynecologic infections (20,21,22 and 23). In an open study of cefotetan (2 to 4 g per day) for the treatment of various pelvic infections (predominantly postpartum endomyometritis and salpingitis), Poindexter et al. (20) reported a clinical cure rate of 99% in 118 patients. Subsequently, Poindexter et al. (21) reported that 93% of 133 patients with obstetric and gynecologic infections responded to cefotetan (2 to 4 g per day). In randomized, comparative clinical trials versus cefoxitin, Hemsell et al. (22) and Sweet et al. (23) reported cure rates with cefotetan (2 to 4 g per day) of 90% and 94%, respectively. The study by Sweet et al. (23) compared cefotetan-doxycycline with cefoxitin-doxycycline for the treatment of acute PID, demonstrating equivalent cure rates (94% and 92%, respectively).

Cefotetan has a serum half-life of 3.5 hours and is administered in a dosage of 2 g every 12 hours. It is excreted primarily by a glomerular filtration and thus dosing must be adjusted in patients with renal failure.

Most hospital formularies consider these two drugs equivalent. Thus, the choice is usually based on cost per day on an institution-by-institution basis.

Because of activity against *N. gonorrhoeae,* including penicillinase-producing species, and anaerobic bacteria, including the *Bacteroides* groups, cefoxitin and cefotetan have been recommended by the Centers for Disease Control and Prevention (CDC) as part of combination therapy for PID and cefoxitin is an alternative choice for uncomplicated *N. gonorrhoeae* (24).

Although cefoxitin has been shown to be effective for prophylaxis, it has no advantage over older less-expensive agents such as cefazolin (25). Because cefoxitin may be used for therapy and is more expensive than older agents, its use for prophylaxis has been questioned. (The use of prophylactic antibiotics is discussed more fully in Chapter 24, Antibiotic Prophylaxis in Obstetrics and Gynecology.) Because of its activity against *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* cefuroxime is commonly used in the treatment of community-acquired bacterial pneumonia (6). Oral second-generation cephalosporins (cefuroxime axetil, cefaclor, cefprozil, and loracarbef) are used to treat various mild to moderate community-acquired infections, including skin and soft tissue infection and UTI (6). However, more cost-effective or narrow-spectrum treatment is available for these indications. Thus, the primary use of oral second-generation cephalosporins is for the treatment of respiratory tract infections.

In summary, among the second-generation cephalosporins, cefoxitin and cefotetan have the most appropriate antimicrobial spectra for treating pelvic infections. They are well tolerated and achieve high concentrations in serum. In most clinical trials, efficacy has been very good. Cefoxitin or cefotetan is a reasonable initial choice for pelvic infections such as endomyometritis, salpingitis, and cuff cellulitis after

hysterectomy.

Third-Generation Cephalosporins

This group of antibiotics is made up of a number of parenteral agents with an even more extended spectrum of activity (26) (Table 23.6). Modification of the side chains provides these new antibiotics with changes in spectrum and alterations in metabolism. In general, the third-generation cephalosporins are less active than the first-generation agents against Gram-positive cocci but are significantly more active against the Enterobacteriaceae. The third-generation cephalosporins are not as active against the *B. fragilis* group of bacteria, as are cefoxitin and cefotetan. On the other hand, they are more active against a broader spectrum of Gram-negative aerobic and facultative bacteria. In addition, as noted in Table 23.5 and Table 23.6, several of these agents have antipseudomonal activity.

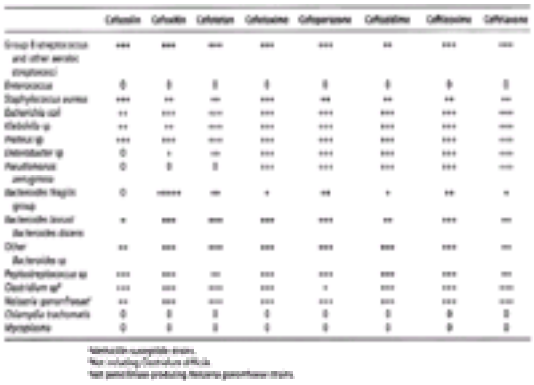


TABLE 23.6. ANTIBIOTIC SENSITIVITIES OF COMMON PATHOGENS RECOVERED FROM OBSTETRIC AND GYNECOLOGIC INFECTIONS

Spectrum of Activity

Although all of these new compounds possess very broad activities, they should not be considered to be interchangeable. Particularly in regard to the array of organisms involved in pelvic infections, there are important *in vitro* differences in activity.

For aerobic streptococci, these agents have activity that is inferior to that of penicillin G or ampicillin and the first-generation cephalosporins. Within the group of third-generation cephalosporins, cefotaxime, ceftizoxime, and ceftriaxone have greater intrinsic activity than cefoperazone and ceftazidime. Yet, with usual doses, all of these agents provide sufficient coverage for all aerobic streptococci except enterococci.

For *S. aureus,* an antistaphylococcal penicillin (such as nafcillin) or a first-generation cephalosporin (cephalothin or cefazolin) would be preferable, because the newer agents have 10- to 80-fold less activity. The MIC_{90} values for these new agents range from 2 to 16 µg/mL, compared with 0.2 µg/mL for cefazolin, but satisfactory

coverage is still supplied by usual doses of the new antibiotics. However, with the exception of ceftazidime, these agents are effective against methicillin-sensitive *S. aureus.* Methicillin-resistant staphylococci are not susceptible to the new agents.

Activity against *N. gonorrhoeae* is excellent, with MIC_{90} values of less than 0.1 µg/mL for cefotaxime, ceftazidime, cefoperazone, and moxalactam. All of these inhibit penicillinase-producing species. Although not quite as active, the MIC_{90} for cefotetan against *N. gonorrhoeae* is 0.5 µg/mL. Among the third-generation cephalosporins, ceftriaxone has the best activity against *N. gonorrhoeae,* including PPNG strains (24,27).

Activity of these agents against aerobic Gram-negative rods is impressive. MIC_{90} values of most of these agents for *E. coli, K. pneumoniae,* and *P. mirabilis* are less than 0.5 µg/mL, but for cefoperazone, the MIC_{90} is 16 µg/mL for the first two species. *Enterobacter* species have higher MIC_{90} values, but these are generally within the susceptible range. The exception is that for *E. cloacae,* the MIC_{90} of cefoperazone is 32 µg/mL. Many aminoglycoside-resistant strains are susceptible to low concentrations of the third-generation cephalosporins. *P. aeruginosa* occurs infrequently in pelvic infections, and activity of these new agents varies widely. Ceftazidime is the most active (MIC_{90} = 8 µg/mL), with cefoperazone and moxalactam having moderate activity (MIC_{90} = 32 µg/mL). For cefotaxime, the MIC_{90} is 64 µg/mL. Other *Pseudomonas* species are likely to be resistant.

Gram-positive anaerobic cocci are inhibited by the third-generation cephalosporins. MIC_{90} values for *Peptococcus* species and *Peptostreptococcus* species were less than 1 µg/mL in the early 1980s (28,29). In 1991, susceptibility of *Peptostreptococcus* species remained good to representative third-generation cephalosporin drugs. For cefonicid and ceftizoxime, 90% of isolates were susceptible to 16 and 8 µg/mL, respectively (8). *C. perfringens* usually has low MIC values, whereas *Clostridium difficile* is resistant.

Among the anaerobic Gram-negative species, *P. bivia* and *P. disiens* are inhibited by 4 to 8 µg/mL of cefoperazone and cefotaxime, but the *B. fragilis* group has a more variable response. Cuchural et al. (9) found that only 59% of strains were inhibited by 16 µg of cefotaxime and only 46% by 16 µg of cefoperazone. For moxalactam, 85% of strains were inhibited by 16 µg/mL. With ceftizoxime, 63% of *B. fragilis* group strains were sensitive to 16 µg. For cefotetan, only 74% of strains were sensitive at 16 µg and 86% at 32 µg. For comparison, metronidazole and chloramphenicol inhibited 100% of *B. fragilis* group strains at 8 µg and 8 µg/mL, respectively. There was 5% resistance to clindamycin at 4 or 8 µg in this study (9). Cefoxitin inhibited 95% of these strains at 16 µg/mL (9).

In general, ceftazidime and ceftriaxone have poor activity against the *B. fragilis* group. This limits their usefulness as single-agent therapy for polymicrobic pelvic infections. Considerable controversy exists over the activity of ceftizoxime against the *B. fragilis* group. The differences were related to variability in the susceptibility test conditions. As noted already, Cuchural et al. (9) reported that one third of *B. fragilis* group bacteria were resistant to ceftizoxime. More recently, Wexler et al. (10) reported modest activity of cefonicid and ceftizoxime against *B. fragilis* species (only 8% and 37% susceptible, respectively, at 32 µg/mL). For other *Bacteroides* species,

activity is greater for cefonicid and ceftizoxime (57% and 93% susceptible, respectively, at 32 µg/mL) (10). In this report, metronidazole and chloramphenicol maintain excellent activity (MIC_{90} = 4 and 8 µg/mL, respectively, for *B. fragilis,* and 16 and 8 µg/mL, respectively, for other *Bacteroides* species).

None of these agents are active against either *C. trachomatis* or the genital mycoplasmas.

Dosage, Route, and Metabolism

Until recently third-generation cephalosporins were available only for parenteral administration. More recently, oral forms have become available. They possess different routes of metabolism and different half-lives.

Cefotaxime has a relatively short half-life of 1 hour and should be administered every 6 to 8 hours. After a 2-g infusion over 30 minutes, peak levels of 80 to 90 µg/mL are attained. By 6 hours, the level is approximately 5 µg/mL. It is excreted mainly in the kidney, by tubular excretion and glomerular filtration. In renal insufficiency, cefotaxime does not accumulate, but the desacetyl derivative, which is not active biologically, has a longer half-life.

Cefoperazone has a longer half-life of 1.6 to 2.4 hours. After a 2-g intravenous dose, serum levels equal 250 µg/mL. At 12 hours, levels are 1 to 2 µg/mL. Accordingly, cefoperazone has been used with dosing every 8 or 12 hours. In contrast to most cephalosporins, this agent is cleared mainly by biliary excretion and does not accumulate in patients with renal failure.

The serum half-life of ceftazidime is nearly 2 hours. It is 10% protein bound, and 80% to 90% of the drug is excreted unchanged by the kidneys in the first 24 hours. The usual dosage is 1 to 2 g every 8 to 12 hours, and the dosage must be adjusted for patients with renal failure. For ceftizoxime, the serum half-life is approximately 1.7 hours, and the drug is excreted unchanged in the urine. Ceftriaxone is dosed at 2 g every 8 hours. Ceftriaxone is a long-acting drug with a serum half-life of 6 to 9 hours, which is the longest of any cephalosporins. The usual dosage for moderate to severe infections is 1 to 2 g intravenously every 12 to 24 hours. Newly introduced oral third-generation cephalosporins include cefixime (Suprax), cefpodoxime proxetil (Vantin), and ceftibuten (Cedax). Investigational oral third-generation agents include cefdinir (Omnicef). With a single oral dose of 400 mg, the peak serum concentration of cefixime is 3.9 µg/mL. The half-life is 3.7 hours. Thus, cefixime is provided as a single daily dose of 400 mg. Cefpodoxime proxetil achieves a maximum serum concentration of 4 µg/mL after a 400-mg oral dose. However, its half-life is 2.2 hours and cefpodoxime proxetil is dosed at 400 mg every 12 hours. With ceftibuten, peak serum levels of 15 to 17 µg/mL are achieved after a dose of 400 mg orally. Its half-life is 2.5 hours. The dose for adult infections is 400 mg as a single daily dose.

Cost

All of the third-generation cephalosporins have a high direct cost per gram, with a cost per day of about $25 to $35 or more. However, because of less frequent doses and more safety, they probably have lower indirect costs (such as pharmacy and

nursing time and tests to monitor safety).

Use in Pregnancy and Placental Transfer

Data on the use of antimicrobial agents during pregnancy, particularly their pharmacokinetics and placental transfer, are limited. Thus, it is not surprising that only a few studies have assessed the use of third-generation cephalosporins during pregnancy. Evaluating placental transfer of cefotaxime, Kafetzis et al. (30) reported serum levels in women undergoing mid-trimester abortion of 8.2 μg/mL at 1 hour after 1-g intravenous infusion and 0.9 μg/mL at 3 hours after infusion. The corresponding mean cord level at 1 hour was 1.9 μg/mL (23% of maternal levels). The serum levels were lower than expected for a nonpregnant woman. Cefotaxime was also found in breast milk in low concentrations (mean, 0.35 μg/mL) (30). In patients in their mid trimester, Giamarellou et al. (14) studied the kinetics of moxalactam and ceftazidime (1-g infusion). For ceftazidime, peak values occurred 2 hours after the infusion and were 13.2 μg/mL. At 6 hours after infusion, the serum levels averaged 1.9 μg/mL. In amniotic fluid, ceftazidime levels ranged from 1 to 4 μg/mL from 2 to 6 hours after infusion. Thus, for ceftazidime, serum levels in pregnant women are nearly 50% of those in nonpregnant women.

Cefoperazone differs from the other cephalosporins in that it has a dual excretory pattern, primarily via the biliary tract and secondarily via the kidney. Although significant alterations occur in renal function during pregnancy, only minimal changes occur in biliary function. Gonik et al. (31) reported that the serum half-life (152 minutes) and the total clearance (1.1 ± 0.4 mL/kg per minute) for cefoperazone in pregnant women were similar to those seen in nonpregnant women. In addition, the trough level of cefoperazone was similar to that seen in nonpregnant women. This is in contrast to the findings for other cephalosporins. Approximately 45% of an intravenous dose of cefoperazone is transferred across the placenta (32). Only minimal transfer of cefoperazone occurs into breast milk, with a mean concentration of 0.3 μg/mL after a 1-g intramuscular dose (30).

Kafetzis et al. (33) evaluated the pharmacokinetics of ceftriaxone in pregnant women. Despite its high protein binding (85% to 95%), ceftriaxone rapidly reached umbilical cord, amniotic fluid, and placenta concentrations in the clinically relevant range. The serum half-life for ceftriaxone was lower in pregnant women than in nonpregnant women.

The elimination rates of ceftriaxone from fetal tissues were almost identical to those from maternal serum. This finding differs from those seen with other antibiotics, which tend to accumulate in the fetus. These authors reported that low concentrations that were only 3% to 4% of maternal serum levels of ceftriaxone occurred in breast milk (33).

Side Effects

In general, adverse effects with these new agents are similar to those seen with older cephalosporins, but there have been several special problems (26). As with the first- and second-generation cephalosporins, hypersensitivity reactions are the most common systemic adverse reactions seen with the third-generation drugs. Allergic reactions, rashes, local pain, and phlebitis have been reported infrequently. They

probably occur in a similar frequency as with first-generation cephalosporins, but comparative studies have not been performed.

Diarrhea has been observed in 1% to 7% of patients receiving these compounds. Because cefoperazone is mainly excreted into the bile, it might be anticipated that it would cause diarrhea more often, but this has not been the case.

Two special adverse effects have been seen with some of these new antibiotics: bleeding and a disulfiram reaction. Hypoprothrombinemia and bleeding have been associated with the use of moxalactam, cefoperazone, cefotetan, and cefamandole (34,35,36,37,38,39,40,41 and 42). These drugs have in common the presence of a MTT side chain on their molecule (38,39 and 40). The MTT side chain has been demonstrated to inhibit gamma carboxylation of glutamic acid, which is the vitamin K–dependent step in the synthesis of prothrombin (39,40). To date, this adverse effect has been reported to occur most frequently with the use of moxalactam (37), a drug no longer available. Most likely, the ability of moxalactam to also interfere with adenosine diphosphate–induced platelet aggregation is responsible for this greater risk for clinical bleeding. Bleeding due to moxalactam generally developed in patients with the following risk factors: renal or liver disease, poor nutrition, use of anticoagulants or aspirin, or thrombocytopenia. Obstetric-gynecologic patients would rarely have any of these risk factors. Kline et al. (41) reported that cefotetan also resulted in a statistically significant increase in prothrombin time in healthy volunteers. Hypoprothrombinemia and bleeding diathesis have been associated with cefotetan therapy (42).

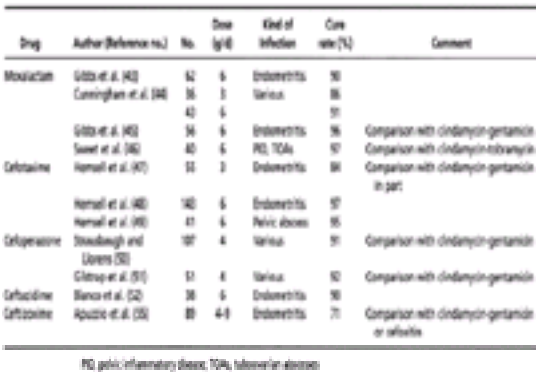
Also seen with moxalactam, cefoperazone, and cefotetan has been a disulfiram reaction (38,41), that is, acute alcohol intolerance due to inhibition of acetaldehyde dehydrogenase. This reaction has been seen in patients taking the antibiotics before alcohol, but not in intoxicated individuals who are treated with these antibiotics. The cephalosporins associated with disulfiram-type reactions also all contain the MTT side chain. Other adverse effects including mild elevation of liver enzymes and neutropenia have occurred infrequently and have been mild and transient.

Because of their very broad spectra, superinfection may result. Enterococcal and candidal infections have been reported, but the incidence is low. In obstetric-gynecologic patients, particularly those who develop infection after prophylaxis with a first-generation cephalosporin, enterococci are isolated frequently, usually in mixed culture. Nevertheless, most of these patients respond promptly to these new antibiotics. Development of resistance during therapy has been seen with *P. aeruginosa* and *E. cloacae.* In debilitated patients, this has led to failure of therapy. In obstetric-gynecologic patients, colonization with resistant organisms has been noted with other antibiotics, but in healthy patients receiving short courses of therapy, poor clinical response has not been attributed to the development of resistance. When response has not been satisfactory and when enterococci are present, it is appropriate to use antibiotic therapy active against this organism.

Indications in Obstetrics and Gynecology

In view of their broad *in vitro* activity, these agents have been used in a number of trials as single-agent therapy in pelvic infections. Of these compounds, the one most thoroughly evaluated in obstetric-gynecologic infections has been moxalactam. As shown in Table 23.7, reported experience includes more than 200 cases in which a

consistent cure rate of approximately 90% has been achieved (43,44,45 and 46). In a double-blind comparison of moxalactam (6 g per day) and clindamycin-gentamicin for the treatment of post–cesarean section endomyometritis, Gibbs et al. (45) found the regimens to be equivalent. Similarly, Sweet et al. (46) noted excellent results (cure rates of higher than 95%) in a prospective controlled study of moxalactam versus clindamycin-tobramycin in the treatment of PID and tuboovarian abscess. Despite these excellent results, the risk of hypoprothrombinemia and bleeding diathesis has limited the use of moxalactam in obstetrics and gynecology and it is no longer marketed in the United States.



Drug	Author (Reference no.)	No.	Dose (g/d)	Kind of infection	Cure rate (%)	Comment
Moxalactam	Gibbs et al. (45)	62	6	Endometritis	90	
	Cunningham et al. (44)	56	3	Various	86	
		42	6		97	
	Gibbs et al. (45)	54	6	Endometritis	96	Comparison with clindamycin-gentamicin
	Sweet et al. (46)	40	6	PID, TOAs	97	Comparison with clindamycin-tobramycin
Cefotaxime	Hemsell et al. (47)	53	3	Endometritis	84	Comparison with clindamycin-gentamicin in part
	Hemsell et al. (48)	143	6	Endometritis	97	
	Hemsell et al. (49)	41	6	Pelvic abscess	95	
Cefoperazone	Strausbaugh and Llorens (50)	107	4	Various	91	Comparison with clindamycin-gentamicin
	Gilstrap et al. (51)	51	4	Various	92	Comparison with clindamycin-gentamicin
Cefoxitin	Blanco et al. (52)	38	6	Endometritis	90	
Ceftizoxime	Aguilar et al. (53)	89	4-8	Endometritis	71	Comparison with clindamycin-gentamicin or cefoxitin

PID, pelvic inflammatory disease; TOAs, tuboovarian abscesses

TABLE 23.7. CLINICAL TRIALS WITH THIRD-GENERATION CEPHALOSPORIN ANTIBIOTICS IN PELVIC INFECTIONS

Cefotaxime has been evaluated by Hemsell et al. in several reports (47,48 and 49). As with moxalactam, a higher cure rate has been seen with 6 g per day than with 3 g per day (97% vs. 84%; $p < 0.05$). Of the total of 143 women treated with the larger doses, there were 5 failures. Of these, two responded to the addition of other antibiotics and three required surgical drainage. In one phase of these studies, cefotaxime was compared with clindamycin-gentamicin. No difference in rates was found.

These same investigators have evaluated cefotaxime in 53 cases of PID and 21 posthysterectomy infections. The cure rate was 96% for PID and 100% for the 21 other infections (48). More recently, Hemsell et al. (49) reported that cefotaxime (2 g every 8 hours) resulted in clinical cure in 39 (95%) of 41 patients with pelvic abscesses. Despite these excellent results, there is a high rate of resistance in the *B. fragilis* group to cefotaxime (9). This drug, though, is a reasonable single agent in most polymicrobial pelvic infections.

In an open noncomparative study, Strausbaugh and Llorens (50) reported that cefoperazone achieved a clinical cure in 97 (91%) of 107 patients with various pelvic infections. Gilstrap et al. (51) compared cefoperazone with a combination of clindamycin-gentamicin in the treatment of obstetric and gynecologic infections. They demonstrated clinical cure in 47 (92%) of 51 patients treated with cefoperazone and 48 (94%) of 51 patients in the clindamycin-gentamicin group. The high rate of resistance to cefoperazone among the *B. fragilis* group limits the usefulness of

cefoperazone as a single agent for the treatment of severe pelvic infections.

Studies of the effectiveness of ceftizoxime in the management of pelvic infections are limited. Both Harding et al. (53) and Lou et al. (54) demonstrated good clinical results in patients with pelvic and intraabdominal infections treated with ceftizoxime. However, Apuzzio et al. (55) reported clinical cure in only 49 (72%) of 68 patients with post–cesarean section endomyometritis treated with ceftizoxime (2 g intravenously every 12 hours) and 15 (72%) of 21 patients treated with ceftizoxime (3 g intravenously every 8 hours), compared with 28 (88%) of 32 patients receiving clindamycin-gentamicin and 15 (62%) of 24 patients receiving cefoxitin. These authors advised caution with the use of single-agent cephalosporins in the treatment of post–cesarean section endomyometritis. However, they used a 48-hour treatment time, rather than 72 hours to determine failure.

Clinical studies of ceftriaxone as single-agent therapy in obstetric and gynecologic infections have not been reported. This is not surprising, because its lack of *in vitro* activity against *B. fragilis, B. bivius,* and *B. disiens* limits its use as a single agent in mixed anaerobic-aerobic infections of the pelvis. On the other hand, ceftriaxone (125 mg intramuscularly) is the drug of choice for uncomplicated anogenital gonorrhea. Ceftriaxone results in cure rates of 98% to 100% for uncomplicated anogenital and pharyngeal gonorrhea, both penicillin-sensitive and PPNG strains. In addition, ceftriaxone-doxycycline has been the primary outpatient regimen for acute PID during the past 15 years (24).

In general, none of these agents have an extensive enough spectrum of activity to warrant its use in septic shock or similar serious infections. When the organism is known, other antibiotics are often preferable, as in staphylococcal or streptococcal wound infections. Although these agents may be effective for prophylaxis, there is no evidence that they are more effective than older less-expensive antibiotics. Indeed, it seems unwise to use them for prophylaxis.

Accordingly, some of these agents would seem to be reasonable choices in the moderate polymicrobial infections commonly seen on obstetric-gynecologic services. These infections include endometritis after cesarean section and pelvic cellulitis after hysterectomy.

For PID, all of these agents yield a high immediate cure rate, particularly in patients without a tuboovarian abscess. Yet, because none of these antibiotics are active against *C. trachomatis,* they must be combined with an antimicrobial agent with activity against *C. trachomatis* (i.e., tetracycline, azithromycin, erythromycin). Although it is not possible to discern a differential effect from clinical studies, the third-generation cephalosporins with somewhat better spectra are moxalactam and possibly ceftizoxime in preference to cefotaxime and cefoperazone. Side effects in obstetric and gynecologic patients are seen infrequently and are mild, by and large.

The cost of these agents is considerable. Decisions regarding the use of these versus a combination with an excellent efficacy (such as clindamycin-gentamicin) must take this aspect into consideration.

Fourth Generation Cephalosporins

Cefepime (Maxipime) is the first of the fourth-generation cephalosporins to become Food and Drug Administration (FDA) approved in the United States. The fourth-generation cephalosporins differ from third-generation agents because of a positively charged quaternary ammonium side chain on the cephem nucleus. This combines with the negative charge on the cephem nucleus to produce a zwitterion effect, which allows for increased penetration via porin channels through the outer membrane of Gram-negative bacteria (1,6). As a result, these agents have broad antimicrobial activity, including against *P. aeruginosa* and organisms producing many b-lactamases (6). Cefepime is active against a wide range of Gram-positive and Gram-negative bacteria (56). Its antipseudomonal coverage is similar to that seen with ceftazidime (56). Cefepime has excellent activity against non–cephalosporinase-producing Enterobacteriaceae such as *E. coli, Klebsiella* and *Proteus* species, *N. gonorrhoeae* and *H. influenzae* (1). Although the MIC values of cefepime against cephalosporinase-producing Enterobacteriaceae such as *Enterobacter, Serratia,* and *Pseudomonas* are higher than those seen with non–cephalosporinase-producing Enterobacteriaceae, it is superior to most third-generation cephalosporins against such bacteria (1). In addition, cefepime demonstrates excellent activity against streptococci, but only moderate activity against methicillin-sensitive *S. aureus.* Cefepime does not have significant activity against the *B. fragilis* group or MRSA.

Cefepime is approved for treatment of uncomplicated and complicated UTIs, skin and soft tissue infections, and pneumonia. It appears to be equivalent to third-generation cephalosporins as therapy for community-acquired pneumonia and UTI (1). However, older less-expensive antibiotics are available for such infections. Cefepime has demonstrated clinical efficacy in the treatment of nosocomial infections (57,58). In particular, cefepime may be superior to third-generation cephalosporins, to which many nosocomial bacteria (e.g., *P. aeruginosa* and Enterobacteriaceae) have become resistant while remaining sensitive to cefepime (1). A combination of cefepime plus metronidazole has been demonstrated to be efficacious in the treatment of severe intraabdominal infections (59).

New Oral Cephalosporins

The first useful oral cephalosporin introduced was cephalexin (Keflex). This was followed by the development of cephradine (Anspor, Velosef, which is no longer available) and cefadroxil (Duricef). All three of these oral cephalosporins have virtually the same antimicrobial activity and are very active against staphylococci, *Streptococcus pyogenes, S. pneumoniae,* and Enterobacteriaceae (some *E. coli, Klebsiella* species, and *P. mirabilis*) (1). Cephalexin and cephradine also have similar pharmacokinetic properties, whereas cefadroxil has a longer half-life, allowing twice-daily dosing. These early oral cephalosporins had poor activity against *H. influenzae* and b-lactamase–producing Enterobacteriaceae. In general, cephalexin and cefadroxil are useful agents for the treatment of UTIs due to susceptible Gram-negative bacteria and minor skin and soft tissue infections due to *S. aureus* and streptococci (2). However, these drugs (particularly cefadroxil) are expensive and are not recommended for routine treatment of UTIs.

Cefaclor was introduced in the late 1970s and had the advantage of activity against *H. influenzae,* including some b-lactamase producers (1). However, 10% to 15% of ampicillin-resistant strains of *H. influenzae* are resistant to cefaclor. The synthesis of

cefuroxime introduced an oral cephalosporin that was resistant to b-lactamases and inhibited many pathogens responsible for respiratory, skin, and UTIs (3). Conversion of cefuroxime to an axetil ester made it orally absorbable. Cefuroxime axetil (Ceftin) is an oral agent with activity against *S. aureus,* groups A and B streptococci, viridans streptococci, and many Gram-negative aerobes including *E. coli, K. pneumoniae, H. influenzae,* and *N. gonorrhoeae* (including b-lactamase–positive strains). Cefuroxime axetil is effective for treating UTIs, skin and soft tissue infection, and upper respiratory infections due to susceptible organisms (2). However, it is also expensive.

Recently, several new oral cephalosporins have become clinically available in the United States. Cefprozil (Cefzil) is an oral second-generation cephalosporin approved for use in the treatment of pharyngitis, bronchitis, otitis media, and skin and soft tissue infections (4,5). Its activity is similar to that of cefaclor and cefuroxime axetil (4), with good activity against methicillin-susceptible *S. aureus,* groups A and B streptococci, *S. pneumoniae, L. monocytogenes, H. influenzae,* and community-acquired Enterobacteriaceae (*E. coli, Klebsiella* species, and *P. mirabilis*). Cefprozil has a half-life of 1.3 hours, which allows once-daily or twice-daily dosing. Like other oral cephalosporins, cefprozil is expensive. Whether it has any unique advantage over other available agents is unclear.

Loracarbef (Lorabid) is an oral b-lactam antibiotic of the carbacephem class. Its *in vitro* activity is similar to that of cefaclor (2,6). Loracarbef is approved for mild to moderate acute bronchitis; pneumonia caused by *S. pneumoniae* or non–b-lactamase-producing *H. influenzae*; otitis media caused by *S. pneumoniae, M. catarrhalis, S. pyogenes,* and *H. influenzae*; pharyngitis or tonsillitis caused by *S. pyogenes*; and acute maxillary sinusitis (2). However, other drugs that are cheaper have similar activities, and the role of this agent awaits further study.

Cefixime (Suprax) is a third-generation cephalosporin that is active against *S. pneumoniae, H. influenzae, Neisseria. catarrhalis, N. gonorrhoeae,* and many of the Enterobacteriaceae (1). *S. aureus* is resistant to cefixime, as is *P. aeruginosa.* Cefixime is more active than other oral cephalosporins against *E. coli, Klebsiella* species, *P. mirabilis,* and *S. marcescens.* This agent has a long half-life of 4 hours and thus can be administered once or twice daily. However, cefixime is expensive and for most indications is not any more effective than less-expensive agents (2). Thus, for otitis media, sinusitis, pharyngitis or tonsillitis, bronchitis, or UTIs, cefixime is an alternative agent but not the first-line choice. Exceptions to this are otitis media due to b-lactamase–producing *H. influenzae* or *M. catarrhalis* and uncomplicated anogenital gonorrhea. For the latter, cefixime has been shown to be as effective in a single dose of 400 mg orally as intramuscular ceftriaxone (7,8).

Cefpodoxime proxetil (Vantin) is another cephalosporin available as an oral agent. It is active *in vitro* against groups A and B streptococci, *S. pneumoniae, H. influenzae* (b-lactamase positive and negative), and *N. gonorrhoeae.* Against *S. aureus,* cefpodoxime proxetil has only modest activity. It is also active against many Enterobacteriaceae but not *Enterobacter, Serratia,* or *Morganella* species (2). Although cefpodoxime has been shown to be effective in the treatment of bronchopneumonia, acute otitis media, pharyngitis, UTI, skin and soft tissue infections, acute and chronic bronchitis, and uncomplicated gonorrhea (2,9), it is expensive and does not offer any advantage over previously available drugs for the treatment of any infection (10). Ceftibuten (Cedax) is the most recently marketed oral

cephalosporin (third generation) in the United States. Its antimicrobial spectrum of activity is limited to streptococci, *H. influenzae* and most Enterobacteriaceae such as *E. coli, P. mirabilis,* and *K. pneumoniae* (1,6). Ceftibuten has poor activity against anaerobic bacteria. Although ceftibuten is clinically effective in the treatment of acute bronchitis, pneumonia (except penicillin-resistant *S. pneumoniae*), acute otitis media and pharyngitis, it provides no significant advantage over the older less-expensive cephalosporins. Table 23.8 summarizes the indications, dosing, and cost of the oral cephalosporins.

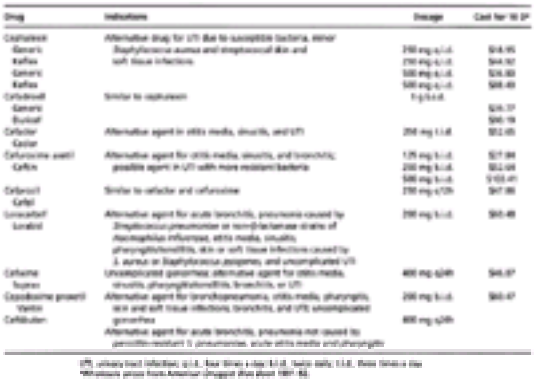


TABLE 23.8. ORAL CEPHALOSPORINS: INDICATIONS, DOSING, AND COST

MONOBACTAMS

Aztreonam is the first monobactam to be clinically available. It has an unusual spectrum in that it is mainly active against the aerobic Gram-negative rods (1). However, it is inactive against Gram-positive organisms or anaerobic bacteria. Yet, like the cephalosporins and penicillins, it has a wide margin of safety and readily achieves therapeutic levels. Aztreonam inhibits most Enterobacteriaceae at levels of less than 0.5 µg/mL. Most *P. aeruginosa* are inhibited by less than 16 µg/mL, but some are resistant. Aztreonam has the advantage of remaining active in an anaerobic environment (e.g., abscess), whereas the aminoglycosides are inactive in anaerobic situations. In addition, aztreonam is not associated with the nephrotoxicity that occurs with aminoglycosides. Hence, this is the potential advantage of these antibiotics over aminoglycosides as drugs of choice in treating Gram-negative infections. In the empiric treatment of pelvic infections, however, aztreonam must be combined with an agent such as clindamycin to provide anaerobic and Gram-positive activity.

Aztreonam is available only in parenteral form. Intravenous boluses of 500, 1,000, and 2,000 mg produced peak serum levels of aztreonam of 58, 125, and 242 µg/mL, respectively (2). Aztreonam is 50% to 70% protein bound. The serum half-life of aztreonam is 1.7 hours, and 60% of the drug is excreted in urine. In the presence of renal failure, aztreonam accumulates, so the dose must be altered accordingly. Aztreonam crosses the placenta and is found in low concentrations in fetal serum and breast milk.

Similar to b-lactam agents, aztreonam is a safe antimicrobial for which no major adverse reactions have been reported. The most common adverse reactions have been rashes and increases in serum transaminase levels.

Aztreonam, in a 1-g intramuscular dose, was noted to be 100% effective for uncomplicated anogenital gonorrhea. However, aztreonam has no activity against *C. trachomatis,* and an agent active against *Chlamydia* must be given concurrently when treating gonorrhea. In treating endometritis, Gibbs et al. (3) compared aztreonam (2 g intravenously every 8 hours) with gentamicin (1.5 mg/kg intravenously every 8 hours), each given with clindamycin. Both regimens were highly efficacious and well tolerated. The aztreonam-clindamycin combination resulted in an 88% cure rate, versus a 91% cure rate with gentamicin-clindamycin. Dodson et al. (4) reported that aztreonam-clindamycin produced clinical cure in 98% of patients with acute PID.

Although the toxicity of aztreonam is clearly less than that of aminoglycosides, obstetric and gynecologic patients are usually at low risk for aminoglycoside toxicity, and aztreonam is considerably more expensive than the aminoglycosides. Potential benefits of the monobactams have to be weighed against their high cost. Thus, aztreonam should be reserved for special situations such as in patients at high risk for aminoglycoside toxicity (e.g., renal disease).

CARBAPENEMS

Carbapenems are derivatives of thienamycin, and currently two of these agents are marketed in the United States: imipenem-cilastatin (Primaxin) and meropenem (Merrem). Imipenem (Primaxin) was the first clinically available member of a new class of antimicrobial agents, the carbapenems. These agents differ structurally from penicillins and cephalosporins. The formulation clinically available is a combination of imipenem and cilastatin, a dipeptidase inhibitor that prevents the nephrotoxicity associated with the use of imipenem alone.

Imipenem has the broadest spectrum of *in vitro* activity of any b-lactam agent (1,2 and 3). This drug has excellent activity against aerobic Gram-positive bacteria, including hemolytic streptococci groups A and B, *S. pneumoniae, Enterococcus,* non-MRSA, and *S. epidermidis. Listeria* is also susceptible. Among the Enterobacteriaceae (*E. coli, Klebsiella, Proteus, Enterobacter*), most are sensitive to imipenem levels of 1 µg/mL or less. Although *P. aeruginosa* is sensitive *in vitro,* resistance to imipenem has emerged during treatment. Imipenem has excellent activity against anaerobic bacteria, including *B. fragilis, B. bivius,* and *B. disiens.* Methicillin-resistant staphylococci, mycoplasmas, and *C. trachomatis* are resistant to imipenem.

Imipenem is 20% protein bound; cilastatin is 40% protein bound. After a 1-g dose of imipenem, peak levels of 70 µg/mL are obtained in serum. The serum half-life of imipenem is approximately 1 hour, and when combined with cilastatin, 70% of the imipenem is excreted unchanged in urine. No studies are available on transplacental transfer or breast milk levels for imipenem.

In an open noncomparative study, Berkeley et al. (4) reported that imipenem resulted

in clinical cure in 43 (88%) of 49 obstetric and gynecologic patients. Three of the failures had pelvic abscesses that required surgical intervention. Of concern was the occurrence of pseudomembranous colitis in two patients. Similarly, Sweet (5) demonstrated the excellent clinical efficacy of imipenem for the treatment of obstetric and gynecologic infections. In this study, clinical response occurred in 70 (97%) of 72 patients treated with imipenem, including all 7 patients with tuboovarian abscesses (documented with ultrasound). In a small comparative study, Berkeley et al. (6) reported a 100% cure rate with imipenem versus a 62% cure rate with moxalactam in the treatment of serious obstetric and gynecologic infections.

As with other b-lactam antibiotics, the most common adverse reactions with imipenem are of the allergy variety in 2% to 3% of patients. Patients who are allergic to penicillin should not be given imipenem. Other reported adverse effects include nausea (1% to 2%), phlebitis and pain at infusion site (2% to 4%), and pseudomembranous colitis (less than 1%). Rarely, seizures have occurred, primarily in elderly patients with underlying CNS disease.

The cost of imipenem remains substantial: approximately $60 per day at a dosage of 500 mg every 6 hours. In view of its unusual spectrum and high cost, it seems best to reserve this drug for special situations including infections with known or suspected resistant pathogens.

Meropenem is the second carbapenem group of antimicrobial agents to become clinically available in the United States. Unlike imipenem, it is stable to dehydropeptidase activity in the kidney (7). Meropenem is slightly more active against Gram-negative bacteria than imipenem. It is active against *P. aeruginosa* resistant to imipenem. Otherwise, its spectrum of activity is very similar to that of imipenem with excellent activity against Gram-positive organisms, Gram-negative aerobes, and anaerobic bacteria. The mean peak serum concentration after a single 500-mg intravenous dose is 30 µg/mL with a half-life of 1 hour. The side effects seen with meropenem are similar to those seen with imipenem, except that meropenem is less likely to produce seizure activity (7).

Clinically, meropenem appears to be equivalent to imipenem and has been used with success to treat pneumonia, meningitis, bacteremia, UTI, intraabdominal sepsis, and febrile episodes in neutropenic patients (7). The recommended adult dosage is 500 mg to 1 g intravenously every 6 to 8 hours.

TETRACYCLINES

All tetracyclines have a similar molecular structure consisting of four benzene rings and generally the same spectrum of activity. The tetracyclines are primarily bacteriostatic. There are two major groups of tetracyclines, which are based on pharmacokinetic properties: short-acting compounds of which tetracycline hydrochloride is the prototype and long-acting compounds, including doxycycline.

Spectrum of Activity

Tetracyclines had a broad spectrum of activity that includes Gram-positive, Gram-negative, aerobic, and anaerobic bacteria, spirochetes, chlamydiae, mycoplasmas, rickettsiae, and even some protozoa. However, because many

organisms have acquired resistance, the role of tetracyclines in obstetric-gynecologic infections is limited, mainly to treating sexually transmitted diseases (STDs) (1,2). The tetracyclines are not drugs of choice for infection caused by Gram-positive aerobes (3).

N. gonorrhoeae and *N. meningitides* had been generally susceptible to tetracyclines. However, increasingly, strains of *N. gonorrhoeae* that are resistant to tetracycline have been reported (4,5). Gonococci resistant to penicillin are likely to be resistant to tetracyclines; approximately 50% of PPNG are resistant to tetracycline as well (5). Not only are PPNG strains resistant to tetracycline, but chromosomally mediated and plasmid-mediated high-level tetracycline-resistant *N. gonorrhoeae* are also a major problem in the United States. Thus, the CDC no longer recommends tetracycline or doxycycline for the treatment of *N. gonorrhoeae* (except as concomitant therapy for *Chlamydia*). Tetracyclines are active against some Enterobacteriaceae such as*E. coli* (particularly community-acquired strains), *Enterobacter,* and *Klebsiella.* However, many Enterobacteriaceae and *Pseudomonas* species are resistant to tetracyclines.

Although the tetracyclines inhibit the growth of many anaerobic bacteria, their activity is not comparable to that of agents such as clindamycin, chloramphenicol, metronidazole, or the newer cephalosporins and extended-spectrum penicillins. Tetracyclines (tetracycline hydrochloride, doxycycline, and minocycline) are the drugs of choice against *C. trachomatis,* mycoplasmas (*Mycoplasma hominis, Ureaplasma urealyticum,* and *Mycoplasma pneumoniae*), and rickettsiae.

Tetracyclines are bacteriostatic. They enter the bacterial organism, where they bind reversibly to the 30S ribosomal unit of susceptible organisms. As a result, polypeptide synthesis is inhibited.

Dosage and Route

Tetracycline hydrochloride and doxycycline are available for administration by the oral, intramuscular, and intravenous routes. The tetracyclines are most commonly administered orally. In Table 23.9, we show the dosing schedule for oral administration of tetracyclines.

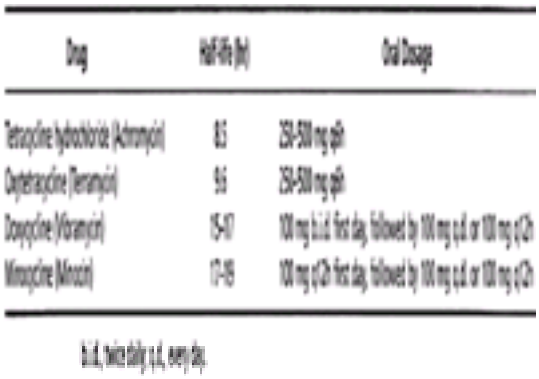


TABLE 23.9. TETRACYCLINES: PHARMACOKINETICS AND DOSING

Of the short-acting forms, tetracycline is the one that is best absorbed, obtains the highest serum levels, and is the least costly. The usual adult oral dosage is 500 mg every 6 hours. Absorption takes place in the proximal small bowel. Peak serum levels of 4 µg/mL are reached 1 to 3 hours after oral administration of a 500-mg dose of tetracycline. After a 500-mg oral dose, oxytetracycline reaches a peak serum level of 2 to 3 µg/mL, and chlortetracycline, 1 to 2 µg/mL.

For doxycycline, the usual adult oral dosage is 100 mg every 12 hours. Doxycycline is almost completely absorbed in the proximal bowel after oral administration. The serum half-life is 18 to 22 hours. After an oral dose of 200 mg, peak serum levels of 2 to 4 µg/mL are attained.

Although available, intramuscular forms of the tetracyclines are irritating and rarely used. After intravenous administration of 500 mg of tetracycline, serum levels reach about 8 µg/mL at 30 minutes and decrease to 2 to 3 µg/mL by 5 hours. Intravenous doxycycline or minocycline in a dose of 200 mg produces a serum level of 4 µg/mL at 30 minutes.

Food of any type markedly reduces the absorption of tetracycline, oxytetracycline, or chlortetracycline. These short-acting agents also have a marked affinity for divalent cations (calcium, magnesium, aluminum), to which they bind and chelate, and thus are excreted in the feces. Tegretol, phenytoin, and barbiturates decrease the normal half-life of doxycycline by almost 50% (3).

Side Effects

The tetracyclines may be associated with local and systemic untoward effects. Allergic reactions including rash, urticaria, and anaphylaxis occur but are uncommon. Photosensitivity reactions associated with onycholysis occur in areas exposed to sunlight. These drugs are irritating, and frequently oral administration produces gastrointestinal symptoms such as nausea, vomiting, and epigastric distress. Diarrhea (including pseudomembranous colitis) may develop, particularly with the forms that are poorly absorbed (i.e., chlortetracycline and oxytetracycline).

Secondary infection with *Candida albicans* is a frequent complication of tetracycline treatment. Tetracycline is deposited in the deciduous teeth of children early in life or if they were exposed as a fetus. The period of mineralization of the decidual teeth commences during the mid trimester of pregnancy and ends 2 to 3 months after birth. Exposure to tetracycline during this time results in yellow discoloration of the “baby” teeth. If tetracyclines are administered to children younger than 6 years, a lifelong discoloration of the permanent teeth may occur. The deposition of tetracycline in the bones of infants causes temporary inhibition of bone growth. A recent case-control analysis did not show any teratogenic potential of doxycycline (6). Nevertheless, tetracyclines should be avoided during pregnancy or while breast-feeding.

A dose-related hepatotoxicity occurs, particularly during the third trimester of pregnancy, with doses of more than 2 g intravenously of tetracycline. It appears

pathologically as “fatty liver” of pregnancy and is associated with a high mortality rate (7). Tetracycline therapy may result in nephrotoxicity as well, either as a result of “acute fatty liver” or by a direct toxic renal effect that aggravates preexisting renal failure. The latter phenomenon results from tetracycline's ability to inhibit protein synthesis, which increases the azotemia from amino acid metabolism.

Minocycline, but not the other tetracyclines, can cause vestibular disturbances with dizziness, ataxia, vertigo, and tinnitus. It is reversible when the drug is stopped. This side effect is much more common in women than in men, occurring in 50% to 70% of women receiving minocycline. As a result of this frequent and bothersome side effect, minocycline is rarely used in female patients.

Cost

Tetracycline is a relatively inexpensive antibiotic. Chlortetracycline, oxytetracycline, doxycycline, and minocycline are more costly for a 7- to 10-day oral course of treatment. However, the cost of doxycycline has recently been lowered.

Use in Pregnancy and Placental Transfer

Tetracyclines cross the placenta and are deposited in decidual teeth and growth centers of long bones, with resultant discoloration of decidual teeth and inhibition of bone growth. Thus, tetracyclines are best not used in pregnancy and while breast-feeding unless alternative drugs are not available.

Metabolism

All the tetracyclines are excreted by the kidneys via glomerular filtration. Nearly 20% of an orally administered dose of tetracycline is excreted in the urine, whereas about 50% of a parenterally administered tetracycline dose is excreted in the urine within 24 hours. Tetracyclines are also excreted in the bile, but a large proportion of this is reabsorbed from the intestine. Except for doxycycline and minocycline, tetracyclines are incompletely absorbed from the gastrointestinal tract, and this unabsorbed drug is excreted in the feces. Both tetracycline and doxycycline should be taken either 3 hours before or 2 hours after taking iron or antacids. The absorption of tetracycline is impaired by food. Thus, tetracycline should not be taken with meals. Doxycycline's absorption is not inhibited by food in the upper gastrointestinal tract (1).

Indications in Obstetrics and Gynecology

Tetracyclines should not be administered to pregnant or lactating women. The major indication for tetracycline in gynecology practice is the treatment of *C. trachomatis* infections, either singly or in combination with other agents depending on the clinical setting (Chapter 3 [Group B Streptococci], Chapter 4 [Genital Mycoplasmas], and Chapter 8 [Mixed Anaerobic-Aerobic Infection and Pelvic Abscess]). Doxycycline is used in the treatment of PID. The tetracyclines are commonly used as prophylactic agents in women undergoing pregnancy termination. In nonpregnant patients allergic to penicillin, it is the alternative drug for the treatment of syphilis. Tetracyclines are the drug of choice against *M. hominis* and *Ureaplasma.* Tetracyclines are also used to treat granuloma inguinale, lymphopathia venereum, actinomyces, and nongonococcal urethritis. In primary care practice, tetracyclines are used to treat

acne and Lyme disease (1).

CLINDAMYCIN

Clindamycin (Cleocin), which is derived from lincomycin, is a macrolide antibiotic. Because of its spectrum of activity, particularly against anaerobes and Gram-positive aerobes, clindamycin is important in treating pelvic infections (1).

Spectrum of Activity

Clindamycin attaches to the 50S ribosome and inhibits bacterial protein synthesis. It is bacteriostatic. Against Gram-positive aerobic organisms, clindamycin has very good activity, including nafcillin-sensitive *S. aureus* and nonenterococcal streptococci. Clindamycin maintains excellent activity against group A streptococci. Approximately 5% of group B streptococci show *in vitro* resistance. Among hospital isolates, 5% to 20% of *S. aureus* isolates are resistant to clindamycin, and MRSA strains are usually resistant. *N. gonorrhoeae* is variably susceptible to clindamycin *in vitro.* However, in combination with aminoglycosides, clindamycin has effectively eradicated *N. gonorrhoeae.* The entire group of aerobic Gram-negative bacilli are highly resistant.

Its activity against the anaerobic organisms provides clindamycin with its main value. With the exception of very few strains of *Clostridium* species and a few strains of *Bacteroides* species, anaerobic organisms are susceptible to this antibiotic. Cuchural et al. (2) reported that 5% of *B. fragilis* group organisms were resistant to clindamycin during 1984 and 1985. However, more recent reviews have demonstrated a prevalence of resistance among *B. fragilis* group bacteria, as high as 20% to 25% in some geographic areas (3,4). Clindamycin is active against *M. hominis* but not *U. urealyticum.*

Clindamycin has very good *in vitro* activity against *C. trachomatis* (5). Clinical studies have demonstrated that in large doses, clindamycin has excellent clinical efficacy against *C. trachomatis* (6).

The MIC for susceptible organisms varies from 0.01 to 4 µg/mL.

Dosage And Route

Clindamycin may be administered intravenously, intramuscularly, orally, or intravaginally as a cream. For intravenous or intramuscular administration, clindamycin phosphate is used. For initial treatment of serious infections, the dosage for intravenous injection is usually 600 mg every 6 hours or 900 mg every 8 hours by “piggyback” injection with an infusion over 30 minutes. After a 300-mg infusion over 30 minutes, serum levels peak at 12 to 15 µg/mL and fall to 5 µg/mL in 2 to 3 hours. For intramuscular injection, the maximum dosage is 300 to 600 mg every 8 hours. For oral administration, clindamycin hydrochloride is used, in a dosage of 150 to 300 mg every 6 hours. For treatment of *C. trachomatis* in patients with acute PID, an oral dosage of 450 mg every 6 hours is recommended. Gastrointestinal absorption is impaired with food in the stomach. No reduction is necessary for patients in renal failure, unless it is severe. For patients with liver disease, the dose should be

decreased.

Side Effects

Gastrointestinal Symptoms

Nausea, vomiting, and particularly diarrhea occur fairly commonly during clindamycin therapy. The incidence of diarrhea varies widely in large series, but in obstetric-gynecologic patients, the incidence has been from 2% to 6%.

Pseudomembranous Colitis (Clostridium difficile–*Associated Diarrhea*)

Pseudomembranous colitis was first observed in patients taking lincomycin. Severe diarrhea and pseudomembranous colitis were subsequently reported in the 1970s in patients taking either oral or parenteral clindamycin. The pathogenesis of antibiotic-associated diarrhea was linked primarily to the anaerobic organism *C. difficile.* The diagnosis of *C. difficile*–associated diarrhea (CDAD) should be suspected whenever a patient who has received antibiotic begins to have diarrhea, particularly if accompanied by abdominal cramps and fever. It should be recognized that the onset of CDAD may be delayed for months (7).

Pseudomembranous colitis has been reported as a complication with various broad-spectrum antibiotics, including tetracycline, ampicillin, and the cephalosporin antibiotics, in addition to clindamycin. *C. difficile* is resistant to clindamycin and many other antibiotics. Thus, various antibiotics may eliminate susceptible intestinal organisms and allow *C. difficile,* if present, to proliferate and elaborate its toxin. The organism is susceptible to vancomycin and metronidazole. Practice guidelines for the diagnosis of CDAD are shown in Table 23.10A. Both the American College of Gastroenterology and the Society for Health Care Epidemiology of America recommend that testing be done on a stool specimen for the presence of *C. difficile* or its toxins. The Society for Health Care Epidemiology of America indicates that stool culture is the most sensitive test for CDAD, whereas the *C. difficile* toxin is the most specific and further suggest that for maximal diagnostic sensitivity and specificity, performance of both tests is recommended. The American College of Gastroenterology further recommends that if the results of these tests are negative but diarrhea persists, one or two additional stool samples can be sent for testing with these tests. Proctoscopic examination is now reserved for special situations, for example, when a rapid test is needed, when other test results are delayed, or when the test is not highly sensitive. Although CDAD will resolve in 15% to 25% of patients, antibiotic therapy is indicated. Metronidazole, vancomycin, and other antibiotics have all been shown to be effective in CDAD, but metronidazole is now considered the initial drug of choice. It has comparable efficacy to vancomycin and it has a lower cost. In addition, there is a hypothetical concern about the use of vancomycin primarily in a situation leading to further resistance with organisms such as enterococci. The recommended therapeutic regimen of first choice is metronidazole (250 mg four times daily or 500 mg three times daily for 10 days). (Please see Table 23.10B.) No diagnostic testing is indicated at the end of therapy, but repeated testing is recommended if diarrhea recurs. Although most patients respond to a specific antibiotic therapy, up to 30% of patients will have recurrence of CDAD. This usually occurs within 1 to 2 weeks.

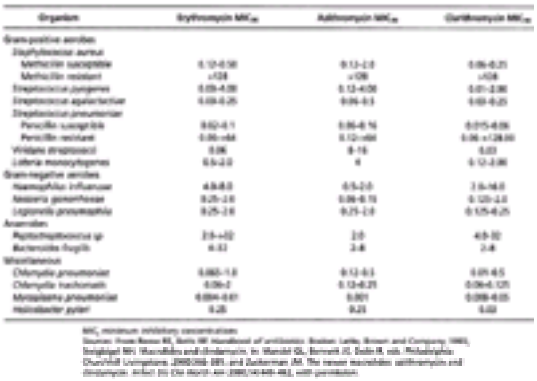


TABLE 23.10. IN VITRO ACTIVITY OF ERYTHROMYCIN, AZITHROMYCIN, AND CLARITHROMYCIN

The practice guidelines for the prevention and control of *C. difficile* infection by the American College of Gastroenterology recommend the following: limiting the use of antimicrobial drugs, washing hands between contact with all patients, using stool isolation precautions for patients with CDAD, wearing gloves when in contact with patients who have CDAD or within their environment, disinfecting objects contaminated with *C. difficile* with appropriate agents, and educating the medical, nursing, and other appropriate staff about the disease and its epidemiology.

For patients who develop diarrhea while receiving antibiotic therapy, we stop suppositories and laxatives and next discontinue clindamycin. If treatment of the *B. fragilis* group is still needed, we will empirically replace it with an alternative agent such as metronidazole. Lomotil and related compounds should be avoided.

Continued use of antibiotics has been shown to prolong the course of the colitis and to worsen the prognosis. Vigorous supportive therapy is essential, but use of Lomotil is dangerous.

Other Side Effects

For the most part, other adverse reactions to clindamycin are rare. Minor elevations in liver function test results (particularly serum glutamic-oxaloacetic transaminase) occur in a small percentage of patients. Allergic reactions such as rash are rare. Occasionally, neutropenia and thrombocytopenia have occurred.

Cost

Both the oral and parenteral preparations of clindamycin remain expensive.

Use in Pregnancy

Although clindamycin carries the standard FDA warning that safety of the use of this

drug in pregnancy has not been established, there is indirect evidence that it is probably safe. In a long-term prospective evaluation of lincomycin in pregnancy, no adverse fetal effects were noted. In view of the close structural similarity of lincomycin and clindamycin, the latter is probably also a relatively safe agent. Thus, pregnancy should not be considered a contraindication to the appropriate use of clindamycin.

Placental Transfer

After intravenous administration to the mother at term, clindamycin rapidly appears in the cord blood. Peak levels are achieved within 20 minutes and are approximately 40% of peak maternal levels. Clindamycin did not appear in the amniotic fluid in detectable concentrations during the first hour after maternal injection.

Metabolism

Clindamycin is removed from the body largely by direct excretion in the bile. A smaller amount is excreted by the kidney, and some is also inactivated in the body, probably in the liver. Clindamycin is excreted in breast milk in small concentrations (1).

Indications in Obstetrics and Gynecology

Clindamycin is a potent and valuable antibiotic, but its use has been accompanied on rare occasion by serious adverse effects. Parenteral clindamycin is indicated in the empiric treatment of pelvic infections such as endometritis, pelvic cellulitis after hysterectomy, PID, tuboovarian abscess, and pelvic abscess. Because these infections are polymicrobial, clindamycin should be used initially in combination with other agents such as aminoglycosides that have activity against Gram-negative aerobic bacteria.

Because of widespread clinical use and consistently high cure rates in many studies, clindamycin plus an aminoglycoside has been considered the standard, against which other antibiotics are measured for the treatment of mixed anaerobic-aerobic pelvic infections (8). Excluding side-effect failures, cure rates with this combination are generally from 90% to 97%.

Oral clindamycin may be used to complete a course of therapy in a patient who has shown a response to parenteral clindamycin, but for most pelvic infections, it is unnecessary to follow parenteral therapy with oral therapy in patients who have responded. Exceptions to this rule are treatment of *C. trachomatis* or abscesses.

Although *S. aureus* is susceptible to clindamycin, it is not the drug of choice for infections caused by these organisms. Penicillinase-resistant penicillins (such as methicillin and others) are preferred, and the cephalosporin antibiotics would be the alternative in most patients with a penicillin allergy. In the rare patient with anaphylaxis to penicillin or a cephalosporin, clindamycin may be used to treat infections with *S. aureus.*

A more recent use of clindamycin is for the treatment of bacterial vaginosis. Both oral clindamycin (300 mg twice daily for 7 days) (9) and clindamycin cream (2%

intravaginally twice daily for 5 days) (10,11) are very effective (equal efficacy to oral metronidazole) for the treatment of bacterial vaginosis. Clindamycin is currently listed as an alternative for intrapartum prophylaxis for the prevention of perinatal group B streptococcal infections. Several reports have raised the concern of resistance of group B streptococci to clindamycin. These reports generally indicate that up to 4% or 5 % may be resistant, but resistance rates are considerably higher with erythromycin (12,13).

ERYTHROMYCIN, AZITHROMYCIN, AND CLARITHROMYCIN

Erythromycin

Erythromycin is a macrolide antibiotic composed of a many-membered lactose ring with one or more deoxy sugars attached. Erythromycin is most active in an alkaline medium and is primarily bacteriostatic.

Spectrum of Activity

The antibacterial spectrum of erythromycin is limited. It is active against various aerobic Gram-positive cocci including groups A and B streptococci and *S. pneumoniae. S. aureus* is generally susceptible to erythromycin, but emergence of resistance does occur during treatment (1,2 and 3). Erythromycin is the drug of choice for *C. diphtheriae.* Similarly, it is the drug of choice for *Legionella pneumophila* and *Haemophilus ducreyi.* Erythromycin is also active against *N. gonorrhoeae, Borrelia burgdorferi, L. monocytogenes, T. pallidum,* and *M. pneumoniae.* Many Gram-positive and Gram-negative anaerobic bacteria are inhibited, but by relatively high concentrations. Erythromycin also is active against *C. trachomatis, C. pneumoniae, M. hominis,* and *U. urealyticum.* Table 23.10 compares the *in vitro* activity of erythromycin with that of azithromycin and clarithromycin.

Erythromycin is bound to the 50S ribosomal unit of susceptible microorganisms and inhibits polypeptide synthesis in ribosomal complexes. The drug accumulates 100 times more in Gram-positive than in Gram-negative bacteria.

Dosage and Route

Erythromycin preparations are available for administration by the oral, intramuscular, and intravenous routes. Oral preparations of erythromycin include erythromycin base (E-Mycin), erythromycin stearate (Bristamycin, Ethril, Pfizer, SK-Erythromycin, Erypar, Erythrocin Stearate), erythromycin estolate (Ilosone), and erythromycin ethylsuccinate (Pediamycin, Wyamycin) (1,2,3 and 4).

Erythromycin base is a very bitter, weak base (pK = 8.8). To make it tolerable, enteric coatings have been applied. In some preparations of erythromycin base, gastrointestinal absorption has been erratic, but E-Mycin (Upjohn) is well absorbed in both the fasting and nonfasting state. Mean peak serum levels of E-Mycin are 0.73 µg/mL 5 hours after a single 250-mg dose. Similar levels are achieved in nonfasting subjects. After multiple dosages of 250 mg four times daily, peak levels of 1.5 µg/mL are achieved.

Erythromycin stearate hydrolyzes to erythromycin base in the duodenum, where absorption takes place. After a 250-mg dose in a fasting subject, levels of 0.82 µg/mL are achieved 2 hours later. Multiple doses every 6 hours lead to levels of 1.0 to 1.5 µg/mL in the fasting state. This preparation should be given 1 hour before or 2 hours after meals. When given with meals, erythromycin is destroyed considerably because of longer periods in the stomach and greater exposure to acid. Acceptable bioavailability of this preparation also depends on administration with adequate amounts of water.

Erythromycin estolate is acid stable, and its absorption is unaffected by food. Although this preparation achieves higher levels than erythromycin base or stearate esters, erythromycin estolate is apparently absorbed primarily as the propionate ester, which is not active until hydrolyzed to the base.

Erythromycin ethylsuccinate is tasteless and is reported to be stable in acid. The usual adult dosage is 250 to 500 mg orally every 6 hours.

Because intramuscular administration of erythromycin is associated with extreme pain, the antibiotic should not be administered by this route. Intravenous administration of erythromycin is associated with a significant incidence of thrombophlebitis at the intravenous site. The dosage for this route is usually 500 mg every 6 hours.

Side Effects

The erythromycins have a good safety record but may be associated with both local and systemic untoward effects. Epigastric distress and gastrointestinal upset occur often after oral administration, particularly in pregnant women. Individuals experiencing these symptoms at 500 mg every 6 hours are often able to tolerate 250 mg every 6 hours. Pseudomembranous enterocolitis has rarely been observed. Pain may develop after intramuscular administration. Hypersensitive reactions, manifested by fever, eosinophilia, and skin eruption, may occur.

The only major adverse effect is hepatotoxicity, which has been seen with the estolate and ethylsuccinate esters. This syndrome is not dose related and usually does not occur after the first exposure to the drug. After 1 to 3 weeks of therapy, patients may develop abdominal cramps, nausea, vomiting, jaundice, fever, leukocytosis, and abnormal liver function. All manifestations usually resolve when administration of the drug has been discontinued.

Cost

As an older preparation, erythromycin is a relatively inexpensive antibiotic.

Use in Pregnancy and Placental Transfer

Erythromycin has not been associated with adverse effects on the fetus, but the estolate salt may cause mild hepatotoxicity more commonly in pregnant women than in other adults (5). Approximately 10% of 161 women treated with the estolate ester

in the second trimester had elevated serum glutamic-oxaloacetic transaminase levels. These returned to within the reference range after the antibiotic was discontinued. Erythromycin crosses the placenta but achieves cord blood concentrations of only 6% to 20% of maternal levels (6). Like many other antibiotics, erythromycin may lower urinary estriol levels (7).

Metabolism

When erythromycin is administered orally, 2% to 5% of the antibiotic is excreted in active form in the urine. After intravenous administration, 12% to 15% is excreted in the urine. Erythromycin is concentrated in the liver and is excreted primarily in the active form in the bile.

Indications in Obstetrics and Gynecology

Erythromycin has been indicated for the treatment of staphylococcal and streptococcal infections in penicillin-allergic patients. Recently, recognition of the importance of infections due to *C. trachomatis* broadened the clinical indications for the use of this antibiotic, particularly in pregnancy (when tetracycline is contraindicated). Schachter et al. (8) demonstrated that the treatment of pregnant women with cervical chlamydial infection with erythromycin ethylsuccinate (800 mg three times a day) eradicated *C. trachomatis* from mothers and prevented vertical transmission to their newborns in more than 90% of cases. Erythromycin is also an alternative to tetracycline for the treatment of *Ureaplasma,* but clinical indications for treating this organism are not clear.

M. pneumoniae is among the microorganisms most frequently responsible for the production of lower respiratory infection (“walking pneumonia”) in people 20 to 40 years of age. *L. pneumophila* has been recognized as an important cause of sporadic pneumonia (Legionnaires disease). Erythromycin is the first choice for the treatment of these two organisms.

Erythromycin is no longer recommended for treatment of gonorrhea or syphilis.

Azithromycin

Azithromycin (Zithromax) is the first new azalide antibiotic to be clinically available. Inserting a nitrogen atom into the lactone ring of erythromycin resulted in an agent with unique properties (9). Thus, azithromycin has an expanded spectrum of activity, high and sustained tissue levels of antibiotic (higher than serum levels), and a prolonged tissue half-life (2 to 4 days), which permits fewer doses per course of therapy and a shorter duration of therapy.

Spectrum of Activity

Azithromycin, like erythromycin, is a broad-spectrum antimicrobial agent that is active against Gram-positive and some Gram-negative bacteria, chlamydiae, mycoplasmas, and some spirochetes (1,2 and 3,10,11). Azithromycin is active against strains of *S. aureus,* groups A and B streptococci, *S. pneumoniae,* and coagulase-negative staphylococci that are susceptible to erythromycin. If resistant to erythromycin, strains of these Gram-positive bacteria are also resistant to

azithromycin. In general, azithromycin is twofold to fourfold less active against staphylococci and streptococci.

Although azithromycin is more active than erythromycin *in vitro* against *H. influenzae* and *Neisseria* species, Enterobacteriaceae (*E. coli, Klebsiella* species, *Proteus, Enterobacter,* and *Serratia*) and *Pseudomonas* species are resistant (10). Azithromycin has greater activity than erythromycin against many anaerobes (10). *C. trachomatis, N. gonorrhoeae, M. pneumoniae,* and *B. burgdorferi* are all susceptible to azithromycin. *T. pallidum* and *Toxoplasmosis gondii* also appear to be susceptible (1,2 and 3,10,11). Azithromycin has excellent activity against *H. ducreyi* (2,3).

Dosage and Route

Azithromycin is available in an oral form as a 250-mg capsule. It is recommended that azithromycin be taken in the fasting state (i.e., 1 hour before or 2 hours after a meal). As noted already, azithromycin has the unique property of producing tissue levels that are 10- to 100-fold higher than serum levels (12,13). It is more stable than erythromycin at acid pH and thus is better absorbed from the gastrointestinal tract (37% vs. 25%). The half-life in tissue is 2 to 4 days, so 5 days of therapy (daily dosages) results in therapeutic tissue concentrations of azithromycin for 5 or more additional days after completion of therapy (12,13). In addition, azithromycin is highly concentrated in polymorphonuclear (PMN) leukocytes, and migration of PMN leukocytes to sites of infection may facilitate transport of this agent to the site of infection (12).

Depending on the type of infection, azithromycin is given as single-dose therapy or as a 5-day regimen. For nongonococcal urethritis or chlamydial cervicitis, a single 1,000-mg dose is indicated. A single 2-g oral dose of azithromycin has been shown to be effective for uncomplicated gonorrhea (14). The 5-day regimen is 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 to 5 for a total dose of 1.5 g. This regimen is recommended for upper respiratory infections (e.g., pharyngitis, otitis media, and sinusitis), lower respiratory tract infections, susceptible skin and soft tissue infections (e.g., bronchitis and community-acquired pneumonia) (81–91), and pharyngitis or tonsillitis (second-line therapy) (1,2 and 3). Azithromycin is an effective alternative choice for the treatment of Lyme disease (3). Currently, azithromycin is not recommended for use in pregnant or lactating women. However, it should be safe in these circumstances, and use during pregnancy only awaits studies confirming safety in infants and fetuses.

Side Effects

Azithromycin appears to be well tolerated (15). It has fewer gastrointestinal side effects than erythromycin, but diarrhea, nausea, abdominal pain, and vomiting can occur. With the 1-g and particularly with the 2-g single dose, gastrointestinal side effects are more common. Mild headache or dizziness occurs in approximately 1% of patients. Allergic reactions are rare, as is superinfection with vaginitis. Liver function test results may be minimally elevated on occasion (1).

Unlike erythromycin, azithromycin does not interact with theophylline or warfarin. However, it may interact in a life-threatening manner (like erythromycin) with terfenadine (Seldane) and astemizole (Hismanal), and these agents should not be

used together until clinical studies demonstrate lack of such an interaction (1).

Cost

Azithromycin is expensive (11). The average wholesale cost to the pharmacy for a 250-mg tablet is $8.13, with the single 1-g dose costing $35.52 and the 5-day 1.5-g total dose cost being $48.78 (1). Because only a few tablets are required, azithromycin remains relatively competitive with agents requiring a 10-day course.

Use in Pregnancy and Placental Transfer

Limited data currently exist as to the safety of azithromycin in pregnancy or during breast-feeding. Theoretically, this agent as a macrolide should be safe in these circumstances. The extent to which azithromycin crosses the placenta and the concentration of azithromycin in the fetus and amniotic fluid are unknown. Preliminary studies have confirmed the safety of azithromycin in pregnancy (16,17 and 18).

Metabolism

Most azithromycin remains unmetabolized in the body (12). Approximately 20% of the drug is excreted unchanged in the urine.

Indications in Obstetrics and Gynecology

Azithromycin is indicated for the treatment of chlamydial cervicitis and urethritis as a single 1-g dose (19). This single dose ensures compliance but is expensive. To date, studies have not been published assessing azithromycin in the treatment of acute PID. Unfortunately, the single 1-g dose of azithromycin is not sufficiently effective to recommend it for the treatment of uncomplicated gonorrhea (11,14).

Treatment of mild community-acquired pneumonia and bronchitis in nonpregnant women with the 5-day regimen (total, 1.5 g) of azithromycin is better tolerated than erythromycin and is very effective.

Use of azithromycin in obstetric patients awaits clinical studies confirming its safety in infants and fetuses. Several small studies suggest that azithromycin is an effective and safe treatment agent for chlamydial infection in pregnancy (16,17 and 18). Azithromycin is an alternative agent for *Mycobacterium avium* and toxoplasmosis in patients with acquired immunodeficiency syndrome (AIDS) (Chapter 10, Acquired Immunodeficiency Syndrome [AIDS]). A single 1-g dose of azithromycin is one of the recommended treatments for chancroid (19).

Clarithromycin

Clarithromycin (Biaxin) contains an *O*-methyl substitution at position 6 of the macrolide ring. Except for enhanced activity against *H. influenzae,* its spectrum of activity is similar to that of erythromycin. However, it has better pharmacokinetic properties, resulting in a twice-daily dose regimen (1,2 and 3,20,21).

Spectrum of Activity

Like erythromycin and azithromycin, clarithromycin is a broad-spectrum antimicrobial that is active against Gram-positive and some Gram-negative bacteria, chlamydiae, mycoplasmas, and some mycobacteria (Table 23.10). Clarithromycin is inactive against MRSA. Staphylococci and streptococci resistant to erythromycin are also resistant to clarithromycin. It has only modest activity against anaerobes, and Enterobacteriaceae are resistant. Clarithromycin is more active than azithromycin or erythromycin against *L. pneumophila* and *C. pneumoniae* (2,3). Clarithromycin has excellent activity against *Helicobacter pylori,* the etiologic agent of peptic ulcer disease (2,3).

Dosage and Route

Clarithromycin is available only as an oral agent. Dosing depends on the pathogen and type of infection. For pharyngitis or tonsillitis, the dosage is 250 mg every 12 hours for 10 days, and for sinusitis, it is 500 mg every 12 hours for 14 days. Acute exacerbation of chronic bronchitis or pneumonia due to *S. pneumoniae* is treated with 250 mg every 12 hours for 7 to 14 days. Bronchitis due to *H. influenzae* requires 500 mg every 12 hours for 7 to 14 days. *M. pneumoniae* pneumonia is treated with 250 mg every 12 hours for 7 to 14 days.

Side Effects

Clarithromycin appears to be well tolerated and safe (1). In preclinical trials, only 1% of patients had severe side effects, most of which were gastrointestinal (17). No significant hematologic, hepatic, or renal toxicity was reported (17). The most common side effect is gastrointestinal symptoms, but these are much less frequent than with erythromycin. Like azithromycin and erythromycin, clarithromycin should not be given concomitantly with terfenadine (Seldane) or astemizole (Hismanal). Other medications such as theophylline, carbamazepine, warfarin, triazolam, ergots, and cyclosporine should be used cautiously when given concomitantly with clarithromycin (2).

Cost

Clarithromycin is more expensive than erythromycin. A 10-day course of 250 mg orally twice daily or 500 mg orally twice daily costs about $50 wholesale (1).

Use in Pregnancy and Placental Transfer

There are no adequate and well-controlled studies of clarithromycin in pregnant women. Thus, it should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Clarithromycin, in high doses, during pregnancy has caused cardiovascular anomalies in rats, cleft palates in mice, and fetal growth retardation in monkeys (11).

The most promising use for clarithromycin appears to be in the therapy for *M. avium* complex in patients with AIDS (2,3,11). Clarithromycin (500 mg orally twice daily), in

addition to ethambutol, is the drug of choice for this entity. In patients with AIDS with CD4 counts of less than 100 cells/mm^3, prophylaxis of disseminated *M. avium* complex infection with clarithromycin (500 mg once or twice daily) is effective (22).

Metabolism

Clarithromycin is extensively metabolized in the liver.

Indications In Obstetrics and Gynecology

The role of clarithromycin in obstetrics and gynecology awaits future studies. For most infections, it is an expensive alternative, and whether its convenient twice-daily dosing offsets this cost is unclear.

In pregnant and nonpregnant patients with AIDS with *M. avium* complex disease, clarithromycin may be an appropriate choice of therapy.

AMINOGLYCOSIDES

The aminoglycoside-aminocyclitol antibiotics include streptomycin, kanamycin (Kantrex), gentamicin (Garamycin), tobramycin (Nebcin), amikacin (Amikin), and netilmicin. Streptomycin now has little use, aside from the treatment of tuberculosis, and kanamycin has largely been replaced by newer members of this group. The remaining agents are the most effective against Gram-negative aerobic organisms, but they have a relatively narrow margin of safety (1).

Spectrum of Activity

The aminoglycoside antibiotics are bactericidal agents that induce defective protein molecules by inhibiting the 30S subunit of the ribosome. Resistance to aminoglycosides may develop because (a) penetration of the antibiotic into the bacterial cell is prevented, (b) the bacterial ribosomes are modified to prevent binding of the aminoglycosides, and (c) bacterial enzymes destroy the antibiotics.

Gentamicin is the most widely used member of this group in obstetric-gynecologic practice. It is active against nearly all strains of aerobic Gram-negative bacteria, including *E. coli, Klebsiella* species, indole-positive and indole-negative *Proteus* species, *Enterobacter* species, and *P. aeruginosa.* Widespread use has led to the development of strains of *P. aeruginosa* that are totally resistant to gentamicin. In view of the rarity of infections due to *P. aeruginosa* and other organisms uniquely susceptible to gentamicin (particularly in obstetric and gynecologic patients), less toxic antibiotics can often be used. Moreover, the introduction of new broad-spectrum agents that are safer, such as third-generation cephalosporins and b-lactam agents plus enzyme blockers, has reduced the need for and use of aminoglycosides.

Gentamicin acts synergistically with the penicillins against enterococci.

The antibacterial spectrum of tobramycin is similar to that of gentamicin, with two exceptions. Many strains of *P. aeruginosa* that are resistant to gentamicin are

susceptible to tobramycin. On the other hand, *S. marcescens* is significantly more susceptible to gentamicin than tobramycin. Susceptible organisms have MIC values of less than 4 µg/mL of gentamicin or tobramycin.

Amikacin is a more recently introduced aminoglycoside antibiotic with activity against a wide range of Gram-negative bacteria, including *P. aeruginosa.* Its use is restricted to the treatment of infections produced by organisms resistant to gentamicin and tobramycin.

Spectinomycin is an aminocyclitol antibiotic and not a true aminoglycoside. The primary clinical indication for spectinomycin has been in the treatment of *N. gonorrhoeae,* particularly in pregnant, penicillin-allergic patients, and treatment of uncomplicated anogenital gonorrhea due to PPNG strains. However, the emergence of PPNG strains resistant to spectinomycin and the availability of ceftriaxone, which is cheaper and also effective against pharyngeal gonorrhea, have limited its use. When used for the treatment of uncomplicated gonorrhea, 2 g intramuscularly as a single dose is recommended.

Dosage and Route

Because their principal toxic effects are dose related, dosages of aminoglycoside antibiotics should be based on the patient's weight. For gentamicin and tobramycin, the usual dosage has been 1.0 to 1.5 mg/kg of body weight every 8 hours, and for amikacin, either 7.5 mg/kg every 12 hours or 5.0 mg/kg every 8 hours. These preparations may be administered intravenously or intramuscularly in the same dose. These are approximations only, and blood levels should be determined, particularly in patients with courses longer than 10 days, with renal disease, with use of other nephrotoxic agents, with marked obesity, or with poor clinical response. In addition, many authors recommend that peak and trough levels be obtained after 24 hours of therapy. If these values are in the recommended range, then levels should be repeated every 3 to 4 days. Table 23.11 lists the expected peaks and troughs of the aminoglycosides. In the last 5 years, interest has focused on once-daily dosing with aminoglycosides. The rationale for this approach is (a) efficacy is comparable to every-8-hour dosing regimens, (b) nephrotoxicity and ototoxicity are less than with once-daily dosing, (c) aminoglycosides have a postantibiotic effect on aerobic Gram-negative bacteria, and (d) cost of administration is reduced.

Antibiotic	Peak (µg/mL)	Trough (µg/mL)	Toxic Level (µg/mL)
Gentamicin	6–8	≤0.8–1.2	>10
Tobramycin	6–8	≤0.8–1.2	>10
Amikacin	22–28	<4–6	>35
Netilmicin	6–8	≤0.8–1.2	>10

TABLE 23.11. EXPECTED PEAKS AND TROUGHS OF THE AMINOGLYCOSIDES

AFTER A TYPICAL 8-HOUR DOSE

After a 30-minute intravenous infusion of a typical 8-hourly dose, a concentration of gentamicin or tobramycin of 6 to 10 µg/mL is achieved rapidly, and concentrations fall to 1 to 2 µg/mL within 6 to 8 hours. For once-daily gentamicin therapy dosing, the usual dosage is 4.5 to 7 mg/kg every 24 hours by the intravenous route. It may also be given intramuscularly in selected circumstances. The dosing interval is increased if creatinine clearance initially is less than 60 mL per minute. For monitoring, a single serum level is obtained between 6 and 14 hours after the first dose, and the level is checked on a nomogram. The level is checked on the nomogram and adjustments in the dosing interval are made if necessary. If therapy is continued for more than 4 days, a second sample is obtained. Pregnancy is considered an exclusion for 24-hour dosing because of the rapid glomerular filtration rate. In the puerperium, however, 24-hour dosing appears to be as safe and effective as 8-hour dosing (2,3).

Aminoglycosides are not absorbed after oral administration; oral preparations are intended only for bowel sterilization.

Determining the proper dose for very obese patients has been a problem (4,5,6,7 and 8). Until recently, it has been thought that aminoglycosides were distributed only in extracellular fluid and that dosages should, therefore, be calculated on lean body weight. Accordingly, when obese patients were given an aminoglycoside dose based on total body weight, serum levels were higher than expected. Very recently, however, it has been recognized that obese patients, given a dose based on lean body weight, may have seriously low antibiotic levels, because there is partial distribution into adipose tissue.

Based on recent pharmacokinetic study, it seems best to determine aminoglycoside doses in obese nonpregnant patients as follows:

1. For mildly obese patients (i.e., those with less than 30% excess weight), use total body weight to calculate dose.
2. For moderately obese patients (i.e., those with more than 30% excess weight), use lean body weight plus 40% of weight of adipose tissue.
3. For severely obese patients, do not exceed 150 mg every 8 hours for initial doses.
4. For moderately and severely obese patients, obtain antibiotic levels and adjust dose accordingly.

Pregnancy and the immediate puerperium represent additional situations when it is difficult to estimate the correct dose. Duff et al. (4) and Blanco et al. (5) found “subtherapeutic” peak levels (i.e., less than 5 µg/mL) in approximately one third of postpartum women given 3.0 mg of gentamicin per kilogram of body weight per day and 4.5 mg of tobramycin per kilogram of body weight per day (4,5). Zaske et al. (6) found it necessary to use 3.0 to 11.6 mg/kg per day (in three divided doses) in pregnant women to achieve proper levels in 77 puerperal patients (6). These investigators emphasized the wide interpatient variation and the need to measure serum levels before using these increased doses. A poor correlation was found

between elimination rate of gentamicin and creatinine clearance, but a high correlation was noted between distribution volume and gentamicin elimination. The latter point suggested that changes in fluid volumes in pregnancy affected gentamicin kinetics. Zaske et al. (7) also found widely ranging needs for gentamicin in gynecologic patients. In 249 patients with normal renal function (serum creatinine, less than 1.5 mg/dL), the daily dose ranged from 1.9 to 14.0 mg/kg (in divided doses) (7).

Aminoglycosides are excreted by the kidney and must be used with caution in patients with renal disease. In such persons, adjustments in the dose of this antibiotic must be made based on serum concentrations.

Side Effects

The principal toxic effects of all aminoglycoside agents are ototoxicity and nephrotoxicity. A relationship between gentamicin dose and the development of ototoxicity has been noted. Significant factors correlating with ototoxicity are length of therapy, bacteremia, and higher temperature. Ototoxicity related to aminoglycoside administration may involve either the auditory or the vestibular portion of the eighth nerve. The ototoxicity may be unilateral or bilateral and is nearly always irreversible. It also tends to occur late in the course of therapy and may even develop or progress after the antibiotic has been stopped. Patients at high risk for ototoxicity are those who have received a high cumulative dose or a protracted course of aminoglycosides. Ototoxicity defined as greater than 15-dB loss of hearing has been reported in about 20% of patients and is detected clinically in about 2%.

Nephrotoxicity develops in approximately 2% of the patients who receive gentamicin. It ranges from minimal abnormalities of the urine sediment to frank renal failure. In most patients who develop gentamicin-induced nephrotoxicity, renal function gradually returns to normal after the drug has been discontinued.

Neuromuscular blockade is a rare complication of all aminoglycosides. It is dose related and is reversed by anticholinesterases and calcium salts.

Tobramycin possesses the potential to produce both ototoxicity and nephrotoxicity, but a number of recent studies have suggested that the incidence of such untoward effects may be lower than with gentamicin. However, most obstetric patients are at low risk for aminoglycoside toxicity. Accordingly, potentially less nephrotoxicity is not a compelling reason to abandon gentamicin.

Cost

The price of gentamicin has fallen dramatically. Amikacin is the most expensive aminoglycoside. Tobramycin is intermediate in cost.

Use in Pregnancy

More than 35 years ago, hearing loss was reported in children born to women who received streptomycin in pregnancy for the treatment of tuberculosis. Data are not available for other aminoglycosides, but the potential exists for fetal eighth nerve or renal toxicity. Nevertheless, pregnancy should not be considered a contraindication

to the use of aminoglycosides.

Concentrations of aminoglycosides in pregnancy are about 25% lower than expected, probably because of more rapid renal clearance (8). Care should be taken to avoid overdosing. If a pregnant patient does not respond to an aminoglycoside despite *in vitro* susceptibility, the antibiotic concentration should be determined.

Metabolism

As noted already, aminoglycoside antibiotics are excreted mainly by the kidneys, with a small amount being excreted in the bile.

Indications in Obstetrics and Gynecology

Because of their activity against aerobic Gram-negative organisms, aminoglycoside antibiotics are widely used in genitourinary infections, usually in combination with other antibiotics.

Soft Tissue Pelvic Infections

In the treatment of serious soft tissue pelvic infections, the combination of an aminoglycoside with other agents such as clindamycin (or less often, metronidazole) is usually considered the standard. Yet, aerobic Gram-negative organisms are isolated in perhaps only 25% of genital infections, and many of these are susceptible to less toxic antibiotics. Thus, even in serious infections, therapy may be modified on the basis of culture results and clinical response. Because of the potential toxicity, the difficulty in achieving the proper level of aminoglycosides, and the expense and toxicity of combination regimens, there has been a major stimulus to the search for newer, safe single agents for therapy.

Urinary Tract Infection

Although nearly all organisms causing UTI (except enterococci) are susceptible to gentamicin, other agents are usually indicated. Aminoglycosides should be used to treat infections caused by organisms with *in vitro* resistance to less toxic agents. Aminoglycoside antibiotics may also be used in the initial treatment (before cultures are available) of recurrent infection when highly resistant organisms are likely. Similarly, an aminoglycoside can be added to ampicillin or cefazolin for initial empiric therapy of acute pyelonephritis.

METRONIDAZOLE

Metronidazole is a nitroimidazole drug that was initially introduced for the treatment of trichomoniasis. Subsequently, it was used extensively for infections due to *Giardia lamblia* and *Entamoeba histolytica.* Metronidazole is widely recognized as an effective antimicrobial for the treatment of anaerobic infections and bacterial vaginosis (1,2).

Spectrum of Activity

The mode of action of metronidazole is believed that the biologic activity of the drug is related to reduction of the nitro group at the *S* position on the imidazole ring. This mode of action of metronidazole on anaerobic microorganisms requires four steps: (a) entry into the microorganisms, (b) reductive activation of the agent, (c) toxic effect of the reduced products or microorganisms, and (d) release of inactivated end products.

The mechanism of the toxic action exerted by the reduced derivatives of metronidazole is assumed to be due to unstable intermediate products. *N*-(-2-hydroxyethyl)-oxalic acid and acetamide form when metronidazole is reduced. It is possible that these partially reduced intermediates are also responsible for the mutagenicity and carcinogenicity associated with metronidazole. The intracellular target of the toxic action is unclear but believed to be an interaction with DNA or a degradation of DNA. This causes extensive damage to nucleic acids and destroys the organism.

Metronidazole is active against the anaerobic protozoa *Trichomonas vaginalis, E. histolytica,* and *G. lamblia.* Metronidazole resistance in strains of *T. vaginalis* has been rarely reported (3). Usually, this is relative resistance requiring higher doses of metronidazole. Metronidazole is active against only those bacteria with primarily anaerobic metabolism (obligate anaerobes). Of the Gram-negative anaerobic bacteria, *Fusobacterium* and *Bacteroides* species, particularly *B. fragilis* and *Bacteroides melaninogenicus,* are the most susceptible. Among the Gram-positive anaerobes, the *Clostridium* species are the most sensitive; *Peptostreptococcus* and *Eubacterium* species are also frequently sensitive. However, *Actinomyces* and *Bifidobacterium* species are less commonly sensitive. Metronidazole has no significant activity against aerobes or facultative anaerobes. In addition, it has less activity against microaerophilic streptococci. Other microaerophilic bacteria such as *Campylobacter fetus* and *Gardnerella vaginalis* are susceptible to metronidazole.

Dosage and Route

Metronidazole may be administered intravenously, orally, rectally, or vaginally. With oral administration, metronidazole should be taken just after or during a meal. Oral doses range from 2 to 4 g as a single dose or 250 to 750 mg three to four times a day. For treatment of trichomoniasis, the usual recommended dosage is either a single 2-g regimen or 250 mg three times a day for 7 to 10 days. For giardiasis, the dose is 250 mg three times a day for 7 days; for nondysenteric amebiasis, 500 mg three times a day for 10 days; and for dysenteric amebiasis or amebic liver abscess, 750 mg three times a day for 10 days. If oral dosing is used for the treatment of anaerobic soft tissue infections, 500 mg three to four times a day is recommended. In bacterial vaginosis, the recommended dosage is 500 mg twice a day for 7 days.

Intravenously administered metronidazole is available as the hydrochloride salt in 100-mL bottles and buffered with sodium bicarbonate. It can be infused over 20 to 30 minutes. The dosage varies from 250 to 750 mg three to four times a day. In general, intravenous metronidazole is reserved for the treatment of moderate to severe anaerobic infections, and the dose is determined by the severity of the clinical infection. Intravenous administration of 2 to 4 g of metronidazole has been used on

occasion to treat resistant *T. vaginalis.*

In Europe, rectal administration of a 1-g metronidazole suppository has been used in a dosage regimen of 1 g every 8 hours.

Metronidazole vaginal gel (0.75%) is available for the treatment of bacterial vaginosis.

Side Effects

When metronidazole has been used in relatively low doses for short periods, very few side effects occur. However, with administration of higher doses over a more prolonged period, side effects occur more frequently. The most common side effects are gastrointestinal disturbances such as nausea, an unpleasant metallic taste, a furred tongue, and abdominal cramps (1,2). Metronidazole has an Antabuse-like effect, so alcoholic beverages should be avoided while taking metronidazole. CNS symptoms with lower doses include headache, ataxia, vertigo, sleepiness, and depression. With very large doses, reversible peripheral neuropathies have occurred, as well as myalgia, transient encephalopathies, and persistent paresthesia. Other side effects noted even with low-dose therapy are vaginal burning, a disulfiram-like intolerance to alcohol, and the presence of dark red-brown urine. Transitory rashes and leukopenia have also occurred.

Concern had been voiced about the safety of metronidazole because of reports suggesting that it may have mutagenic, carcinogenic, or teratogenic properties. Several reviews have given evidence putting aside concerns of metronidazole induced teratogenesis (4,5).

Recently, attention has been focused on the interaction of metronidazole with other drugs. The concomitant administration of metronidazole augments the hypoprothrombinemic effect of warfarin (Coumadin). On the other hand, diphenylhydantoin (Dilantin) and phenobarbital increase the metabolism of metronidazole.

Cost

Oral metronidazole is not under patent protection any longer and is thus relatively inexpensive. Intravenous metronidazole is a costly preparation.

Use in Pregnancy and Placental Transfer

Metronidazole passes across the placental barrier and can be found in fetal tissue, cord blood, and amniotic fluid in high concentrations. As described already, metronidazole has been used extensively during pregnancy without apparent ill effects (5). In previous editions of the text, we had voiced the precaution that metronidazole should be avoided in the first trimester of pregnancy and that alternative agents should be preferred in the second and third trimesters of pregnancy. Some texts (6) still note that manufacturers do not recommend that metronidazole be used in the first trimester of pregnancy or during lactation and that if the drug is used in the second or third trimester, a large single-dose treatment should be avoided. However, in view of recent reassuring reviews, as noted already,

metronidazole may be used without regard to adverse effects to the pregnancy in the second or third trimester. It is also noted that in the 1998 STD treatment guidelines, metronidazole use in pregnant patients as a 2-gm and a single dose is recommended for the treatment of trichomoniasis, without any restriction about use in the first trimester (7).

Metronidazole is excreted in breast milk and is present in breast milk in levels comparable to those in serum (8). Thus, it has been suggested that either lactating women should not receive metronidazole or that breast-feeding should be temporarily discontinued for 24 hours after a single oral dose of metronidazole.

Metabolism

Metronidazole is almost completely absorbed after oral administration and diffuses well into nearly all tissues, resulting in wide distribution throughout the body. After single oral doses of 250 and 500 mg, peak serum levels of 6 and 12 µg, respectively, have been reported. Oral 500-µg doses of metronidazole administered four times daily resulted in peak serum levels of 20 to 50 µg/mL. The peak blood levels achieved with intravenous metronidazole approximate those of the oral route. After inserting a 1-g suppository, a mean serum level of 2.3 µg/mL was detected at 1 hour and 10.5 µg/mL at 4 hours. The serum half-life of metronidazole is about 8 hours.

Metronidazole binds to plasma protein in the range of 20%. In humans, it is primarily eliminated through metabolism, which occurs mainly in the liver via oxidation, hydroxylation, or conjugation of side chains on the imidazole rings. Metronidazole is excreted primarily via the kidneys but is found in feces as well.

Indications in Obstetrics and Gynecology

Metronidazole is a potent antimicrobial agent against anaerobic protozoa and bacteria. In the United States, metronidazole is the only effective drug available for the treatment of *T. vaginalis.* Outside the United States, other nitroimidazoles are available. A 2-g single dose and 250 mg three times a day for 7 days are very effective. The FDA has approved a preparation called Flagyl 375 (375 mg twice a day for 7 days) for the treatment of trichomoniasis. Approval is on the basis of pharmacokinetic equivalency of this regimen with metronidazole (250 mg three times a day for 7 days). No clinical data are available to demonstrate the clinical equivalency of these regimens (7). Metronidazole is used for the treatment of amebiasis and giardiasis. It is the drug of choice for amebiasis, and an alternative therapy in giardiasis, where quinacrine is the drug of choice.

Bacterial vaginosis is a synergistic polymicrobial infection associated with *G. vaginalis* and anaerobic bacteria, particularly *Peptococcus* and *Bacteroides* species. Metronidazole (500 mg orally twice daily for 5 days) or metronidazole vaginal gel 0.75% (one application once or twice daily) is effective therapy for bacterial vaginosis.

The important role of anaerobic bacteria in soft tissue infections of the upper genital tract of women is well recognized, with anaerobes recovered from approximately two thirds of pelvic infections. With the recognition of the excellent bactericidal activity of metronidazole against anaerobic bacteria, it has been used widely as a therapeutic

agent in the treatment of infections associated with anaerobic bacteria. For this type of infection, 250 to 750 mg three to four times a day is the recommended dosage. Because these infections are generally mixed infections involving facultative bacteria and anaerobes, metronidazole must be used in combination with an agent effective against Gram-negative facultative bacteria, such as an aminoglycoside. However, this combination does not provide activity against facultative streptococci such as group B streptococci, which are common pathogens in the obstetrics and gynecology. Thus, an agent such as ampicillin or penicillin must often be added. Alternative regimens with metronidazole include combining it with second- or third-generation cephalosporins or monobactam antimicrobial agents. However, this results in a rather expensive combination.

In the treatment of intraabdominal and pelvic infections, therapeutic trials comparing a metronidazole combination with a clindamycin combination have failed to demonstrate an enhanced clinical efficacy for metronidazole (9,10). Because metronidazole has not resulted in an enhanced clinical efficacy over current standard therapies and because concern exists about its carcinogenic potential, metronidazole should not be considered a first-line antimicrobial agent for treating mixed aerobic-anaerobic pelvic infections. Rather, it should be used as a backup agent when other treatment regimens have failed or when anaerobes resistant to clindamycin, chloramphenicol, or cefoxitin are present. However, many authorities disagree and suggest that metronidazole is the drug of choice for the treatment of anaerobic infections.

A multitude of inexpensive antimicrobial agents are available for use as prophylactic antibiotics in surgical procedures. These agents are not required for treating severe infection and make ideal prophylaxis choices. It seems inappropriate to use metronidazole as a prophylactic antibiotic at this time (1).

FLUOROQUINOLONES

During the past decade, the new quinolone antimicrobial agents have aroused great interest. The quinolone agents act on bacterial DNA gyrase, an enzyme that helps maintain the structure of DNA and thus inhibit DNA synthesis. Nalidixic acid (NegGram) was the first quinolone introduced into clinical practice. Although it possesses *in vitro* activity against many Enterobacteriaceae, nalidixic acid is weakly active against *Pseudomonas* species and Gram-positive organisms. In addition, nalidixic acid achieved low serum levels after oral administration, had poor tissue penetration, led to rapid development of resistance during therapy, and led frequently to adverse CNS effects (1,2,3,4 and 5). Thus, its use has been limited to treatment of UTIs (1,2).

In an attempt to expand the spectrum of activity of nalidixic acid and the clinical usefulness of quinolones, several derivatives of nalidixic acid were developed. However, cinoxacin (Cinobac) and oxolinic acid (Utibid) did not provide any real clinical advantages over nalidixic acid and were also classified as urinary tract antiseptics (6).

Over the past 15 years, various fluorinated derivatives of nalidixic acid have been developed and investigated. Addition of a fluorine molecule at position 6 of the basic quinolone nucleus enhanced the spectrum of quinolone activity 1,000-fold and increased penetration into bacterial cells (3,7). Five of these

fluoroquinolones—norfloxacin (Noroxin), ciprofloxacin (Cipro), ofloxacin (Floxin), lomefloxacin (Maxaquin), and enoxacin (Penetrex)—became clinically available by the early 1990s. As the new millennium commenced, six new fluoroquinolones—levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, moxifloxacin, and gatifloxacin—have been approved for clinical use in the United States (3,4). Additional new fluoroquinolone agents such as clinafloxacin, temafloxacin, and tosufloxacin should soon be available. These compounds have a markedly expanded spectrum of activity compared with nalidixic acid. In addition, their pharmacokinetic characteristics allow their use in various systemic infections.

Spectrum of Activity

The fluoroquinolones, like nalidixic acid, kill susceptible bacteria by inhibiting DNA synthesis secondary to a direct effect on DNA gyrase (1). The spectrum of activity of the fluoroquinolones is wide. As shown in Table 23.12, these new fluoroquinolones are much more active than nalidixic acid.

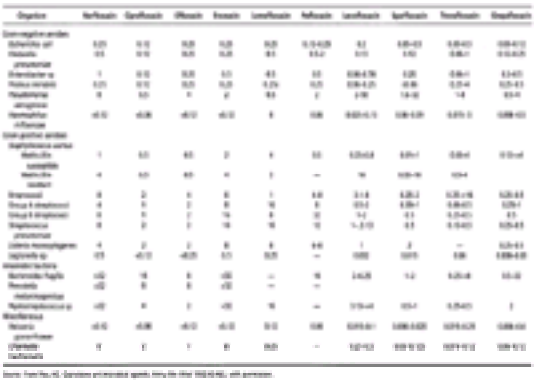


TABLE 23.12. IN VITRO ACTIVITY OF THE QUINOLONE ANTIBIOTICS: MIC_{90} (µg/mL)

Enterobacteriaceae are highly susceptible to the fluoroquinolones with MIC values of 0.5 µg/mL or less. In addition, these compounds are active against *P. aeruginosa.* The fluoroquinolones also have excellent activity against other Gram-negative bacteria such as *H. influenzae* and *N. gonorrhoeae* including PPNG strains. Gastrointestinal pathogens such as *Shigella* species, *Salmonella* species, *Campylobacter jejuni, Vibrio* species, and *Yersinia enterocolitica* are highly susceptible to these new fluoroquinolones (1,6,9,10 and 11).

The older fluoroquinolones—norfloxacin, ciprofloxacin, and ofloxacin—are active primarily against a wide variety of aerobic Gram-negative bacteria, including Enterobacteriaceae, *H. influenzae, Neisseria* species, *Campylobacter* species, and *M. catarrhalis* (3). These older agents also have activity against *P. aeruginosa,* with ciprofloxacin being the most active (8). However, an increasing number of studies have demonstrated higher MIC levels at or above susceptibility breakpoints of the older fluoroquinolones of *Klebsiella* species, *Enterobacter* species, *S. marcescens,*

and *E. coli* (8). Although the newer fluoroquinolones with enhanced activity against Gram-positive bacteria have maintained their excellent Gram-negative aerobic coverage, they have lost activity against *P. aeruginosa* (3).

The MIC values against Gram-positive bacteria are generally higher than those against Gram-negative organisms. The older fluoroquinolones have relatively high MIC values against streptococci (1,6,9). However, streptococci and enterococci are susceptible at levels achievable in the urine. Although the older fluoroquinolones have only modest activity against Gram-positive bacteria, the newer fluoroquinolone agents have enhanced activity against these agents (3,4). Thus, newer fluoroquinolones such as grepafloxacin, sparfloxacin, trovafloxacin, gatifloxacin, and moxifloxacin have MIC_{90} values ranging from 0.25 to 0.5 µg/mL against methicillin-susceptible *S. aureus* (8). Levofloxacin is somewhat less active. Gatifloxacin, sparfloxacin, and trovafloxacin also have some activity against MRSA (Table 23.12). Other staphylococci species (e.g., *Staphylococcus saprophyticus* and *S. epidermidis*) are also susceptible to the newer agents (8). The newer fluoroquinolones all are active against *S. pneumoniae* (8). Most importantly, the MIC values of the new fluoroquinolones are similar for both penicillin-susceptible and penicillin-resistant strains (12,13). As a result, the newer fluoroquinolones have become popular agents for the treatment of community-acquired lower respiratory tract infections (bronchitis and pneumonia) (3). However, Chen et al. (14) recently reported the occurrence of decreased susceptibility of pneumococci to fluoroquinolones between 1988 and 1998 in association with increased prescribing of these agents. Close monitoring of this trend will be required. The newer fluoroquinolones are also active against *S. pyogenes* (group A b-hemolytic streptococci) and *Streptococcus agalactiae* (group B b-hemolytic streptococci). On the other hand, activity against enterococci remains variable even among the newer fluoroquinolones, with sparfloxacin and gatifloxacin being most active (3).

In general, the MIC values against anaerobic bacteria for the older fluoroquinolones are even higher than those against Gram-positive bacteria (6,9,10 and 11). Thus, the older quinolones have limited anaerobic activity. Among the newer fluoroquinolones, only trovafloxacin has been approved by the FDA for the treatment of anaerobic infections. Although gatifloxacin, moxifloxacin, sparfloxacin, and clinafloxacin have demonstrated activity against anaerobic bacteria in vitro, few clinical treatment trials have been reported (3,4,15).

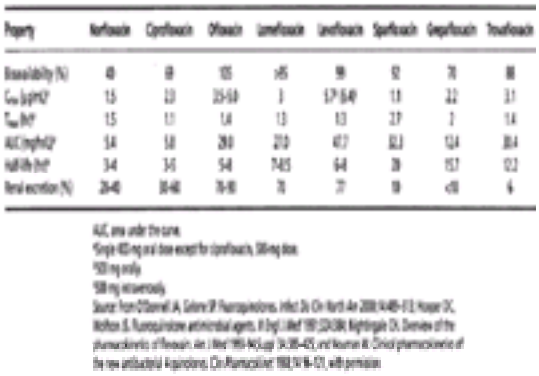
The older fluoroquinolones have demonstrated variable *in vitro* activity against *C. trachomatis* (7,8 and 9). Only ofloxacin is recommended for the treatment of *C. trachomatis* infections among the older quinolones (8). In addition, these fluoroquinolones have activity against other intracellular organisms such as *L. pneumophila, U. urealyticum, M. hominis, M. pneumoniae, M. avium,* and *Mycobacterium intracellulare.* All of the newer fluoroquinolones have activity against *C. trachomatis, C. pneumoniae, U. urealyticum, M. hominis,* and *M. pneumoniae* (3,4,8). All of the newer agents also have excellent activity against *L. pneumophila* (19).

Unfortunately, the initial view that bacterial resistance to the fluoroquinolones would not be a significant problem has proven to be unfounded. Clinically important resistance to the fluoroquinolones is an increasing problem with *S. aureus, P. aeruginosa,* and *S. marcescens* (10,11,20,21). Nearly 80% of MRSA strains reported to the CDC were resistant to ciprofloxacin, with prior exposure to ciprofloxacin being

a major risk factor (22). Similarly, increasing resistance (10% to 30%) is being reported with methicillin-susceptible *S. aureus* (10,11). The CDC has also reported the occurrence of decreased susceptibility of *N. gonorrhoeae* to the fluoroquinolones.

Dosage and Route of Administration

In addition to the increased bacterial spectrum provided by the fluoroquinolones, the pharmacokinetic characteristics of these new compounds have significantly enhanced their clinical usefulness. The pharmacokinetic characteristics of these agents are compared in Table 23.13. Norfloxacin has poor oral bioavailability, achieves lower peak concentrations than other quinolones, and is not useful for systemic infections. Other fluoroquinolones are well absorbed orally with a bioavailability of more than 50% for all agents and approaching 100% for several (Table 23.13) (4,25,26). Although norfloxacin and ciprofloxacin undergo hepatic metabolism and are eliminated by both hepatic and renal mechanisms (27), ofloxacin and lomefloxacin are metabolized to a lesser degree and are primarily excreted by the kidneys (26,28). Thus, ofloxacin and lomefloxacin achieve higher peak concentrations and larger areas under the time-concentration curve.



Property	Norfloxacin	Ciprofloxacin	Ofloxacin	Lomefloxacin	Levofloxacin	Sparfloxacin	Grepafloxacin	Trovafloxacin
Bioavailability (%)	40	69	100	>85	99	92	78	88
C_{max} (μg/ml)[a]	1.5	2.5	2.5-5.0	3	5.7[b]-8.0	1.8	2.2	3.1
T_{max} (hr)[a]	1.5	1.1	1.6	1.5	1.3	2.7	2	1.4
AUC (mg/ml·hr)[a]	5.4	5.8	28.0	27.9	47.7	62.3	12.4	30.4
Half-life (hr)[a]	3.4	3.5	5.4	7-8.5	6-8	20	15.7	12.2
Renal excretion (%)	20-40	30-40	70-80	70	77	19	<10	6

AUC, area under the curve.
[a]Single 400-mg oral dose except for ciprofloxacin, 500-mg dose.
[b]200 mg only.
[c]300 mg intravenously.
Source: From O'Donnell JA, Gelone SP. Fluoroquinolones. Infect Dis Clin North Am 2000;14:485-512, Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. N Engl J Med 1991;324:384; Nightingale CH. Overview of the pharmacokinetics of fleroxacin. Am J Med 1990;88(suppl 5A):3S-8S; and Neuman M. Clinical pharmacokinetics of the new antibacterial 4-quinolones. Clin Pharmacokinet 1988;14:74-121, with permission.

TABLE 23.13. COMPARISON OF PHARMACOKINETIC CHARACTERISTICS OF THE FLUOROQUINOLONES

Among the newer fluoroquinolones, levofloxacin and sparfloxacin are cleared by the kidneys and thus require dosing medication with impaired renal function (29). Hepatic metabolism and biliary excretion are the primary routes of elimination for sparfloxacin, grepafloxacin, and trovafloxacin (3,4).

The pharmacokinetic characteristics of the newer fluoroquinolones are superior to those of the older agents (3). In general, their serum half-lives are longer, which permits once-daily dosing for most newer fluoroquinolones. As a consequence of once-daily dosing, higher peak levels are achieved, which results in maximal bacterial killing (3). The newer agents have an increased volume of distribution, which results in excellent tissue penetration (8). All the fluoroquinolones are bactericidal antimicrobial agents with a concentration-dependent killing effect (3). Thus, the high peak concentrations achieved by fluoroquinolones result in more rapid

and complete killing of susceptible bacteria (3,8). All the fluoroquinolones demonstrate a postantibiotic effect, which is concentration dependent (8). Among the newer fluoroquinolones, this postantibiotic effect lasts for 1 to 6 hours, further enabling these agents to be dosed once daily (3).

One of the major advantages of the fluoroquinolones is that they can be administered orally and are generally well absorbed after oral administration, reaching peak serum concentrations 1 to 2 hours after oral dosing. Maximum serum concentrations achieved after oral administration range from 1.1 to 6.4 µg/mL. These levels are higher than the MIC values of most organisms. Moreover, urinary levels of the fluoroquinolones are very high, up to 100 times the serum concentration. These new fluoroquinolones have low protein binding (15% to 40% protein bound), have large volumes of distribution, and penetrate well into various body fluids and tissues (2,6). Concomitant administration of magnesium- or aluminum-containing antacids reduces the absorption of fluoroquinolones. Antacids should not be taken until at least 2 hours after fluoroquinolone administration (6). Sucralfate reduces the bioavailability of the fluoroquinolones by 85% to 90%; administration more than 6 hours before fluoroquinolones is necessary (6). Ciprofloxacin and enoxacin interfere with excretion of theophylline.

Norfloxacin, ciprofloxacin, ofloxacin, enoxacin, lomefloxacin, pefloxacin, sparfloxacin, levofloxacin, grepafloxacin, moxifloxacin, and trovafloxacin are available in an oral form. Ciprofloxacin, ofloxacin, pefloxacin, levofloxacin, and trovafloxacin also are available as intravenous preparations. In general, these agents provide 1 µg/mL per 100 mg of antibiotic infused intravenously (11).

Although the fluoroquinolones are potent broad-spectrum antibiotics, the *Medical Letter* only lists them as the drugs of choice for UTIs due to *P. aeruginosa, Shigella* infections, and *C. jejuni* infections (30). All of the fluoroquinolones are very effective against most bacteria causing UTIs (Table 23.12). However, it is recommended that the fluoroquinolones not be used for uncomplicated UTI (e.g., cystitis), an infection for which other less-expensive and effective agents are available (Chapter 15, Urinary Tract Infection). For complicated (pyelonephritis) or recurrent UTI, these agents are best reserved for the treatment of more resistant pathogens such as *P. aeruginosa* or other hospital-acquired Gram-negative aerobes. Among the newer fluoroquinolones, only levofloxacin is approved for the treatment of cystitis and pyelonephritis.

The fluoroquinolones provide good to excellent activity against many STDs (Table 23.12) (3,4,31,32). All available fluoroquinolones have excellent activity against *N. gonorrhoeae.* A single oral dose of ciprofloxacin (500 mg) or ofloxacin (400 mg) is effective for the treatment of uncomplicated gonococcal cervicitis, urethritis, or rectal infection. Among the newer fluoroquinolones, trovafloxacin, and grepafloxacin are FDA approved for the treatment of gonococcal infection. However, trovafloxacin is no longer recommended due to its liver toxicity (3). None of the fluoroquinolones is effective in a single-dose regimen against *C. trachomatis.* Of the older fluoroquinolones, only ofloxacin (300 mg orally twice daily for 7 days) has proven consistent efficacy against *C. trachomatis.* All the newer fluoroquinolones have activity against *C. trachomatis* that is equivalent or superior to ofloxacin (3). The most recent CDC guidelines recommend that for outpatient treatment of PID, ofloxacin (400 mg twice daily orally for 14 days) in combination with clindamycin or metronidazole is an alternative for the ceftriaxone or cefoxitin-doxycycline regimen

(31). Against *H. ducreyi* (chancroid), ciprofloxacin (500 mg orally twice daily for 3 days) is effective (32). All the new fluoroquinolones have excellent activity against *H. ducreyi* (3).

Fluoroquinolones are useful agents for the treatment of pneumonia and bronchitis due to susceptible Gram-negative pathogens. However, the older agents should not be used for empiric therapy of common community-acquired pneumonias in which *S. pneumoniae* is the most common pathogen. As discussed already, the newer fluoroquinolones are commonly used agents for treating community-acquired bronchitis and pneumonia. All the fluoroquinolones are excellent agents for the treatment of bacterial gastroenteritis (10,11). These agents are the drugs of choice for *Shigella* infections as a single oral dose or 3 days of therapy (30). These agents are all effective for the treatment of traveler's diarrhea as a 3- to 5-day course. The recommended doses are ciprofloxacin (500 mg every 12 hours), ofloxacin (300 mg every 12 hours), and norfloxacin (400 mg every 12 hours).

The fluoroquinolones are useful agents in treating mixed soft tissue infections. They are effective against the Gram-negative aerobes involved in these mixed infections (e.g., cellulitis, wound infection, and ischemic ulcers), but an agent effective against anaerobes must be added with the older agents.

Table 23.14 and Table 23.15 summarize the dose schedules of the fluoroquinolones. Intravenous therapy is reserved for seriously ill patients who are unable to take oral therapy.

Infection	Ciprofloxacin	Ofloxacin
Urinary tract		
Uncomplicated	250 mg q12h (3 d)	200 mg q12h (3 d)
Complicated	500 mg q12h (7 d)	200 mg q12h (7 d)
Infectious diarrhea	500 mg q12h	300 mg q12h
Lower respiratory, bone and joint, skin and skin structures		
Mild to moderate	500 mg q12h	400 mg q12h
Severe	750 mg q12h	
Acute uncomplicated gonorrhea	500 mg single dose	400 mg single dose
Chlamydia trachomatis cervicitis/urethritis	—	300 mg q12h (7 d)

[a]Oral and intravenous doses are same.

TABLE 23.14. DOSING OF CIPROFLOXACIN AND OFLOXACIN[a]

Pefloxacin	400 mg q12h
Lomefloxacin	400 mg q24h
Sparfloxacin	400 mg loading dose, then 200 mg q24h
Levofloxacin	500 mg q24h
Grepafloxacin	400–600 mg q24h
Trovafloxacin	200–300 mg q24h

TABLE 23.15. DOSING OF NEWER FLUOROQUINOLONES

Side Effects

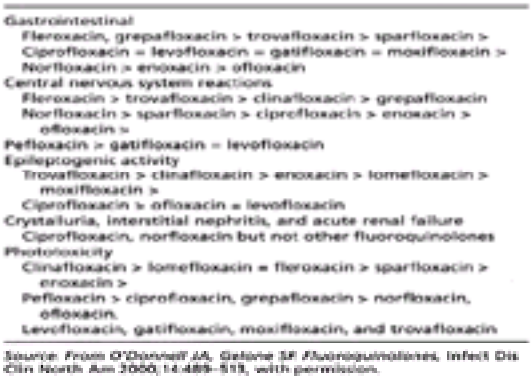
In general, the fluoroquinolones are well tolerated and considered relatively safe compared with other commonly prescribed antibiotics (5,7). Overall adverse reactions among the older fluoroquinolones have been reported in 2% to 8% of patients (10,11,33). The adverse reactions are similar for the various older fluoroquinolones. The most common adverse effects associated with use of quinolones are gastrointestinal (nausea, vomiting, diarrhea, and anorexia) and CNS related (dizziness, headache, and insomnia). In addition, rash and transient elevation in liver enzymes may occur. Quinolones inhibit theophylline metabolism, and their concomitant administration leads to elevated serum theophylline levels.

Adverse events ascribed to the use of fluoroquinolones can be either associated with the chemical and structural modifications made to improve these agents or unrelated to these changes (3). Crystalluria, phototoxicity, genetic toxicity, and drug interaction are toxicities related to chemical modifications, whereas gastrointestinal symptoms and chondrotoxicity/arthropathy are not (3,34). According to O'Donnell and Gelone (3), the most commonly reported adverse events with the use of fluoroquinolones are listed by organ system and their manifestations in Table 23.16. The relative frequencies among the fluoroquinolones for some of the clinically significant adverse events are shown in Table 23.17 (3).

Body System	Specific Adverse Events
Cardiovascular	Hypotension, tachycardia, corrected QT interval prolongation
Dermatologic	Headache, dizziness, sleep disturbances, mood change, confusion, psychosis, tremor, seizures
Gastrointestinal	Nausea, vomiting, diarrhea, anorexia, dyspepsia, abdominal discomfort
Hepatic	Transient raised transaminase levels, cholestatic jaundice, hepatitis, hepatic failure
Musculoskeletal	Arthropathy, tendonitis, tendon rupture
Renal	Azotemia, crystalluria, hematuria, interstitial nephritis, nephropathy, renal failure
Other	Drug fever, chills, serum sickness–like reaction, anaphylaxis, angioedema, bronchospasm, vasculitis

Source: From O'Donnell JA, Gelone SP. Fluoroquinolones. *Infect Dis Clin North Am* 2000;14:489–513, with permission.

TABLE 23.16. COMMON ADVERSE EVENTS ASSOCIATED WITH FLUOROQUINOLONES



Gastrointestinal
- Fleroxacin, grepafloxacin > trovafloxacin > sparfloxacin > Ciprofloxacin = levofloxacin = gatifloxacin = moxifloxacin > Norfloxacin > enoxacin > ofloxacin

Central nervous system reactions
- Fleroxacin > trovafloxacin > clinafloxacin > grepafloxacin
- Norfloxacin > sparfloxacin > ciprofloxacin > enoxacin > ofloxacin >

Pefloxacin > gatifloxacin = levofloxacin

Epileptogenic activity
- Trovafloxacin > clinafloxacin > enoxacin > lomefloxacin > moxifloxacin >
- Ciprofloxacin > ofloxacin = levofloxacin

Crystaluria, interstitial nephritis, and acute renal failure
- Ciprofloxacin, norfloxacin but not other fluoroquinolones

Photoxicity
- Clinafloxacin > lomefloxacin = fleroxacin > sparfloxacin > enoxacin >
- Pefloxacin > ciprofloxacin, grepafloxacin > norfloxacin, ofloxacin.
- Levofloxacin, gatifloxacin, moxifloxacin, and trovafloxacin

Source: From O'Donnell JA, Gelone SP. Fluoroquinolones. Infect Dis Clin North Am 2000;14:489–519, with permission.

TABLE 23.17. SUMMARIES OF ADVERSE EVENT: POTENTIAL ASSOCIATED WITH FLUOROQUINOLONES

Gastrointestinal side effects are the most frequent reported adverse effects associated with fluoroquinolone use (3,4 and 5,7) and have been reported in 0.8% to 11% of patients (5). Nausea is the most commonly reported gastrointestinal side effect (5). An unpleasant taste has been reported in 9% to 17% of patients receiving grepafloxacin (35). This side effect appears to be dose related.

Neurotoxicity is the second most frequent category of adverse effects related to fluoroquinolones (3,4 and 5,7). Overall, CNS reactions have occurred in 0.9% to 11% of patients (3,4 and 5). Mild reactions such as headache, dizziness, tiredness, and sleeplessness are most commonly noted (3,4 and 5). These CNS side effects appear to be more commonly associated with ofloxacin and lomefloxacin than with other fluoroquinolones (5). Severe neurotoxicity is rare (less than 0.5%) and includes psychosis, hallucinations, depression, and seizures (5). These reactions usually commence a few days after beginning treatment with a fluoroquinolone and resolve when the agent is stopped (5). Neurotoxicity is more likely to occur in elderly patients, particularly those with significant arteriosclerosis, and in individuals with CNS impairments (5). It is recommended that fluoroquinolones should not be given to patients with a history of seizures (5).

Allergic and skin reactions occurred in 0.4% to 2.2% of patients (3). Phototoxicity is a potentially significant side effect that must be considered with the clinical use of fluoroquinolones (3,4 and 5,7). Quinolone phototoxicity appears to be related to fluoridation at the 8 position and thus is more common and possibly more severe with lomefloxacin, fleroxacin, and sparfloxacin (5,36). Moderate to severe phototoxicity manifests as an exaggerated sunburn reaction with reddening, blistering, and subsequent peeling of skin (5). Most likely, phototoxicity is an

idiosyncratic reaction, although the risk appears to increase with higher doses and longer courses of fluoroquinolone treatment (5,37). Thus, it is appropriate to warn all patients taking fluoroquinolones of the phototoxicity side effect. It can occur with both direct and indirect sunlight.

Both older and newer quinolones induce arthropathy with cartilage erosions and noninflammatory effusions in the weight-bearing joints of juvenile animals (3,4 and 5). It has been suggested that the pathogenic mechanism responsible for this arthropathy is chelation of magnesium by fluoroquinolones (38). As a consequence of these findings in juvenile animals, concern has been raised over potential cartilage toxicity in children and quinolones have not been recommended for routine pediatric use or for pregnant and lactating women (3,4 and 5). However, there is little evidence of quinolone-induced arthropathy in humans (3,4 and 5,36,39,40). More than 10,000 pediatric cases (many with cystic fibrosis) treated with fluoroquinolones have been reported (40). Concurrent joint disease has been explained in most instances by hyperimmune mechanisms of the so-called cystic fibrosis arthropathy or hypertrophic pulmonary osteoarthropathy. Among the pediatric cases treated with fluoroquinolones, the incidence of arthralgia was no greater than that expected as a result of cystic fibrosis (3). Moreover, none of the fluoroquinolones evaluated had negative effects on linear growth of children (41). Recently, Church et al. (42) assessed sequential ciprofloxacin therapy in 1,795 cases of pediatric cystic fibrosis and noted that there were no unequivocal cases of quinolone arthropathy. Burkhardt et al (43) recently reviewed the clinical treatment of more than 7,000 children and adolescents with fluoroquinolones and did not demonstrate any association with the development of arthropathy. This absence of human arthropathy with increasing exposure of pediatric patients to fluoroquinolones has led some authorities to suggest that in some children, particularly those with cystic fibrosis, the benefits of fluoroquinolones outweigh the small risk of joint toxicity (43,44). Although expanded pediatric use of fluoroquinolones is being considered (43,44), the quinolones are not currently recommended for routine use in children, have not been approved for pediatric use in the United States, and should not be given to nursing mothers (5). In addition, their safety in pregnancy remains to be established (7,45).

Quinolones have also been reported to cause tendonitis and rupture of the Achilles tendon, with more than 200 cases reported in the literature (40). These complications have occurred even with short-term use. Most cases of tendonitis have been associated with pefloxacin with much lower incidences occurring with ciprofloxacin, ofloxacin, norfloxacin, and enoxacin (3).

Post–marketing surveillance of trovafloxacin disclosed an unexpected rare occurrence of adverse hepatic reactions (46). From February 1998 through early May 1999, 2.5 million prescriptions for trovafloxacin were written in the United States and 140 patients were reported to have experienced a hepatic adverse event (incidence rate, 0.0056%). In 14 of the cases, the FDA determined that acute liver injury was strongly associated with concomitant administration of trovafloxacin (5,46). Of these cases, four patients required liver transplantation (one subsequently died) and five patients died. Although the hepatic reactions occurred between 1 and 60 days after commencing treatment, the risk of serious hepatic injury increases with more than 14 days of trovafloxacin therapy (5). As a result of these adverse events, it has been recommended that trovafloxacin use be limited to serious infections in hospitalized patients with concurrent monitoring of hepatic enzymes (46). This has limited the usefulness of trovafloxacin in obstetric and gynecologic patients,

particularly for STDs and PID in which the drug held great promise.

Prolongation of the QT interval has been reported in patients receiving sparfloxacin and to a lesser degree grepafloxacin (47). Other fluoroquinolones have not been associated with this side effect. Hemolytic anemia associated with renal failure, coagulation disorders, or both have been rarely reported except with temafloxacin, which was removed from the market when post–marketing surveillance identified an incidence of 1 in 5,000 prescriptions (4). Ocular side effects of fluoroquinolones include blurred vision, diplopia, photophobia, abnormal accommodation, and changes in color perception (5). These symptoms resolve once therapy is halted (7).

The safety of quinolones in pregnancy has not been established. However, preliminary reports of babies born to pregnant women exposed to norfloxacin or ciprofloxacin during the first trimester have not demonstrated any increased teratogenic risk (48,49). Teratogenicity studies have not identified gross structural defects such as limb reductions in association with fluoroquinolone use (35). Prenatally formed cartilage appears to be much less sensitive to fluoroquinolones than joint cartilage (5). Moreover, reproductive toxicity studies with ciprofloxacin in animals did not demonstrate any effect on fertility or on prenatal or postnatal development (36). Similarly, no embryonic or teratogenic effects were noted in animal studies (36).

Certain precautions are advised with the use of fluoroquinolones (10,11,33,50). They should not be used in patients allergic to nalidixic acid. Because these agents produce cartilage erosions in young animals, the fluoroquinolones should not be used in children and are not recommended for use in pregnant or lactating women. The exact age above which quinolones are safe is debatable. The CDC recommended quinolone use in adolescents 17 years of age or older. One exception is cystic fibrosis in children, where the benefit of fluoroquinolones outweighs the potential risks. Significant interactions between the fluoroquinolones and other drugs have been reported (Table 23.18). Antacids with magnesium or aluminum markedly decrease oral absorption. Theophylline levels must be monitored, because its metabolism is diminished by fluoroquinolones. Ciprofloxacin and enoxacin also interfere with caffeine metabolism.

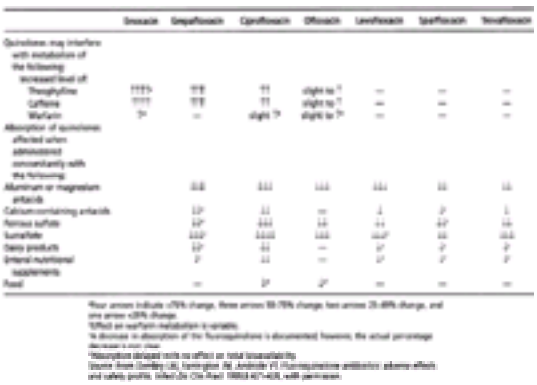


TABLE 23.18. FLUOROQUINOLONES AND INTERACTIONS WITH OTHER DRUGS AND FOOD

Coadministration of drugs containing aluminum, magnesium, iron, and calcium may result in significant decreased bioavailability of fluoroquinolones (3). Thus, products containing any of these cations should be staggered, so the fluoroquinolone agent is administered 2 hours before or after the offending agent (3). Clearance of theophylline is reduced by enoxacin, ciprofloxacin, clinafloxacin (investigational), and grepafloxacin, resulting in significantly increased levels of theophylline (enoxacin, 84%; ciprofloxacin, 30%) (3). Acute theophylline toxicity may occur and is characterized by nausea, vomiting, and rarely seizures (3). These are expensive antibiotic agents and should be used only when clearly indicated. Moreover, inappropriate or excessive use of the fluoroquinolones is an emerging concern (10,11,33). In addition to the cost issue, their overuse is leading to resistance, particularly among *S. aureus* and *P. aeruginosa.*

Cost

The fluoroquinolones are significantly more expensive than trimethoprim-sulfamethoxazole, sulfisoxazole, or ampicillin for the treatment of acute UTIs. However, these agents are very cost-effective when used to treat UTIs due to resistant organisms such as *P. aeruginosa* that would otherwise require parenteral therapy. Similarly, despite its expense, ciprofloxacin is very cost-effective as an oral agent for the treatment of osteomyelitis due to susceptible organisms. As noted already, overuse of these agents must be avoided.

Use in Pregnancy

Animal studies have demonstrated that the quinolones are deposited in cartilage and result in irreversible arthropathy (6). Moreover, these agents work by inhibiting DNA synthesis. Thus, these agents are not recommended for use in pregnant or lactating women. However, clinical studies have not confirmed such findings (48,49).

Indications in Obstetrics and Gynecology

To date, the fluoroquinolones have found their greatest use in treating uncomplicated gonorrhea, UTIs (particularly those due to multidrug-resistant Gram-negative organisms), and diarrheal diseases due to *Shigella* species, *Salmonella* species, or *C. jejuni* (3,4 and 5,51,52,53 and 54). Ofloxacin is effective for the treatment of chlamydial cervicitis and urethritis.

The fluoroquinolones have undergone clinical investigation in the treatment of acute PID. Crombleholme et al. (55) reported that ciprofloxacin (300 mg intravenously every 8 hours) for the treatment of acute PID resulted in clinical cure in 31 (94%) of 33 patients with acute PID, compared with 34 (95%) of 35 patients treated with clindamycin-gentamicin. However, as a single agent, ciprofloxacin was much less effective than the clindamycin regimen in eradicating anaerobic bacteria from the endometrial cavities of these patients. The clinical significance of this finding is not clear, but such a finding suggests that ciprofloxacin may not be useful as a single agent for the treatment of acute PID. Ofloxacin as a single agent for the treatment of PID has been clinically effective, particularly when *N. gonorrhoeae* is the predominant organism (56,57). The lack of anaerobic coverage is problematic

though. As noted already, the fluoroquinolones are not recommended for use in pregnant or lactating women.

VANCOMYCIN

Vancomycin (Vancocin) is a glycopolypeptide that is unrelated to any of the other antimicrobial agents. It has a narrow spectrum of activity and is bactericidal. Vancomycin inhibits synthesis and assembly of cell wall peptidoglycan polymers. Until recently, vancomycin was limited to use as an alternative agent against enterococci and penicillin-resistant staphylococci in penicillin-allergic patients. However, the emergence of methicillin-resistant staphylococci and antibiotic-associated colitis due to *C. difficile* has led to a dramatically increased clinical role for vancomycin, which is the drug of choice for the former and an alternative for the latter condition (1,2).

Both *S. aureus* and *S. epidermidis* are susceptible to vancomycin, with MIC values ranging from 1 to 5 µg/mL. Similarly, group A and group B b-hemolytic streptococci and *S. pneumoniae* are highly susceptible. Generally, the enterococcus is inhibited by concentrations of vancomycin that are obtainable in the serum with parenteral therapy. Since the mid-1980s, however, acquired vancomycin resistance in enterococci has begun to appear (1). According to data from the CDC, vancomycin resistance has increased more than 20-fold, from less than 0.5% in 1989 to more than 10% in 1995. Fortunately, from the viewpoint of obstetrics and gynecology, nearly all of the vancomycin-resistant enterococci are species other than *Streptococcus faecalis.* In other words, they are enterococcal species that rarely occur in obstetric and gynecologic patients. Nevertheless, the concern of vancomycin-resistant enterococci heightens overall concern regarding the development of antibiotic-resistant bacteria. *C. difficile* and *C. perfringens* are usually susceptible. All strains of methicillin-resistant staphylococci are susceptible to low concentrations of vancomycin, although some strains have demonstrated tolerance to its bactericidal action (1).

Vancomycin is given intravenously in 100 to 250 mL of 5% dextrose in water or 0.9% saline over 30 to 60 minutes. The usual intravenous dose of vancomycin is 1 g every 12 hours or 500 mg every 6 hours. The dose must be reduced in the presence of renal disease. For the treatment of *C. difficile* enterocolitis, an oral dose of 125 to 500 mg every 6 hours is recommended. Rapid or bolus administration is dangerous and contraindicated; it can result in extreme flushing and anaphylactic reactions. Vancomycin is poorly absorbed orally and is used by the oral route only for the treatment of enterocolitis. After intravenous administration of a 500-mg dose, peak serum levels of 50 µg/mL are obtained, and serum levels of 6 to 10 µg/mL occur at 1 to 2 hours. Vancomycin is excreted almost entirely via the kidney, and 80% to 90% of the drug appears in the urine within 24 hours. From 10% to 55% of the drug is protein bound. The serum half-life is about 6 hours. With renal failure, the dosage must be reduced.

Most serious toxicity effects such as nephrotoxicity associated with vancomycin in the past were due to impurities present with the active drug. With the currently available purified preparations, adverse reactions are significantly less frequent. The most commonly reported side effects associated with vancomycin are fever, chills, and phlebitis at the infusion site. With too rapid infusion of the drug, tingling and flushing may occur. Most importantly, shock has been reported to occur with rapid

intravenous infusion of vancomycin. Allergic reactions occur in 4% to 5% of patients. The most important adverse reaction to vancomycin is neurotoxicity, which presents with auditory nerve damage and hearing loss. However, with serum concentrations less than 30 µg/mL, this complication is infrequent. Although vancomycin no longer carries a significant risk for nephrotoxicity, high doses of vancomycin should be avoided, and when used in conjunction with an aminoglycoside, the dose of vancomycin should not exceed 0.5 g every 8 hours. Serum levels of vancomycin can be monitored. With a 1-g dose, peak levels of 20 to 50 µg/mL and troughs of 5 to 10 µg/mL are expected.

The major uses of vancomycin include treatment of (a) methicillin-resistant staphylococcal infections, (b) enterococcal endocarditis in penicillin-allergic patients (in combination with an aminoglycoside), and (c) antibiotic-associated *C. difficile* colitis. In addition, vancomycin is recommended by the American Heart Association for use as a prophylactic agent to prevent bacterial endocarditis in penicillin-allergic patients undergoing certain dental or surgical procedures. Vancomycin is not contraindicated during pregnancy or the puerperium. During pregnancy, the indications and cautions for its use are similar to those in nonpregnant patients.

SULFONAMIDES AND TRIMETHOPRIM-SULFAMETHOXAZOLE

Sulfonamides were the first antimicrobial agents introduced into clinical practice in the 1930s. Shortly after Prontosil became available, it was recognized that its antibacterial activity was due to sulfanilamide. Subsequently, hundreds of sulfanilamide derivatives, the sulfonamides, were synthesized. More recently, trimethoprim was developed and found to be a potentiator of sulfonamide activity.

The sulfonamides that are currently available are divided into short-acting, medium-acting, and long-acting sulfonamides (Table 23.19). In addition, there are sulfonamides limited to the gastrointestinal tract (poorly absorbed) and topical sulfonamides. These drugs are bacteriostatic and inhibit bacterial growth by interfering with bacterial synthesis of folic acid. This action occurs because sulfonamides competitively inhibit the incorporation of *p*-aminobenzoic acid into tetrohydroopteroic acid. Trimethoprim inhibits bacterial dihydrofolate reductase, the enzyme step in the synthesis of folic acid immediately after the step blocked by sulfonamides.

Short- or medium-acting sulfonamides
Sulfisoxazole (Gantrisin)
Sulfamethoxazole (Gantanol)
Sulfadiazine
Sulfamethizole (Microsul, Thiosulfil)
Long-acting sulfonamides
Sulfadoxine (combined with primethamine = Fansidaar)
Sulfonamides limited to gastrointestinal tract
Sulfaguanidine
Sulfasuxidine
Sulfathalidine
Sulfasalazine (Azulfidine)

TABLE 23.19. CLASSIFICATION OF THE AVAILABLE SULFONAMIDES

Initially, the sulfonamides exhibited a broad spectrum of activity against Gram-positive and Gram-negative organisms. However, widespread resistance has developed to these agents. Thus, the primary use of these agents is in the treatment of UTIs due to susceptible bacteria. Most first-episode UTIs are due to susceptible Enterobacteriaceae. For recurrent or chronic UTIs, therapy must be based on *in vitro* susceptibility tests. The most common sulfonamide used for the treatment of UTIs is sulfisoxazole (Gantrisin) in a dose of 1 g orally every 6 hours. Short-acting sulfonamides are safe to use during pregnancy. However, because of concern over competition with bilirubin for binding on albumin, some authorities do not use sulfonamides during the third trimester of pregnancy.

Trimethoprim is active *in vitro* against most Gram-positive cocci and Gram-negative rods, except for *P. aeruginosa.* Most anaerobes are resistant. The action of trimethoprim is potentiated in combination with sulfamethoxazole. The combination of trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra) is active against 90% to 95% of *S. aureus, S. pneumoniae,* group A streptococci, *E. coli, P. mirabilis, Shigella* species, *Salmonella* species, and *N. gonorrhoeae* (1). Almost all *P. aeruginosa* strains are resistant to TMP-SMX.

The major indication for TMX-SMX is the treatment of UTIs. Most Enterobacteriaceae are sensitive to TMX-SMX. The usual adult dosage is two tablets (trimethoprim [80 mg per tablet] and sulfamethoxazole [400 mg per tablet]) every 12 hours or a single double-strength tablet (TMX, 160 mg; SMX, 800 mg) every 12 hours. TMX-SMX is an effective agent for the treatment and prevention of gastroenteritis caused by enteropathogenic *E. coli* and traveler's diarrhea (2,3). Although TMX-SMX can treat chlamydial urethritis and cervicitis, its activity is due to the sulfonamide (4). TMX-SMX has been demonstrated to be effective in the treatment of *Pneumocystis carinii* infections in patients with AIDS. It is the first-line drug for the treatment of and primary and secondary prophylaxis against Pneumocystis carinii pneumonia (PCP) in human immunodeficiency virus–infected patients (5,6). Sulfonamides have been used to treat toxoplasmosis in patients with or without AIDS and chloroquine sensitive of chloroquine-resistant *Plasmodium falciparum* malaria (with pyrimethamine) (7). TMX-SMX use in pregnancy is appropriate when indicated and other agents are not available.

Side effects associated with sulfonamides include nausea, vomiting, diarrhea, rash, fever, headache, depression, jaundice, hepatic necrosis, drug-induced lupus, and a serum sickness–like syndrome (7). Serious adverse effects caused by sulfonamides include acute hemolytic anemia related to erythrocyte glucose-6-phosphate dehydrogenase deficiency, aplastic anemia, agranulocytosis, thrombocytopenia, and leukopenia (7). In addition, significant hypersensitivity reactions occur with administration of sulfonamides; examples include erythema nodosum, erythema multiforme (including Stevens-Johnson syndrome), vasculitis, and anaphylaxis.

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24

ANTIBIOTIC PROPHYLAXIS IN OBSTETRICS AND GYNECOLOGY

Because infections have been nearly an every day encounter in a busy obstetric-gynecologic practice, there has been great interest in antibiotic prophylaxis for operative procedures in the specialty. Over the last three decades, a large body of data has accumulated to allow for the establishment of practical recommendations for use in many procedures. Quality standards have very recently been published for antimicrobial prophylaxis in all surgical procedures (1). In previous editions of this book, this chapter included detailed tables listing numerous publications and giving specific results of these individual tables. Because these studies are now aging and because antibiotic prophylaxis is so well established for many procedures, we have decided to eliminate these detailed and cumbersome tables and replace them with practice recommendations.

There are special conditions regarding the use of antibiotic prophylaxis in an obstetric-gynecologic population. First, nearly all obstetric and most gynecologic patients are healthy and free of serious underlying disorders. Second, because the lower genital tract is a contaminated field, operation through or adjacent to this field leads to a moderate to high incidence of infection (in the absence of antibiotic prophylaxis), but serious infection measured by abscess or death is unusual. Third, use of certain antimicrobials for prophylaxis in pregnancy is often contraindicated because of the potential for adverse effects on the fetus, newborn, or mother. In this chapter, *antibiotic prophylaxis* is defined as the use of antibiotics for the prevention of infection in the absence of current signs or symptoms of infection.

USES IN OBSTETRICS

In obstetric patients, most attention has been directed at prophylaxis of the patient undergoing cesarean delivery. Antibiotic prophylaxis for prevention of perinatal neonatal group B streptococcal infection and for use in patients having premature or

prolonged rupture of the fetal membranes is discussed in Chapter 3 (Group B Streptococci) and Chapter 19 (Subclinical Infection as a Cause of Premature Labor), respectively.

Cesarean Delivery

As noted in Chapter 20 (Postpartum Infection), cesarean delivery is accompanied by more frequent and more serious puerperal infections. Indeed, cesarean delivery is the single most important risk factor for maternal postpartum infection. Patients undergoing cesarean delivery have a 5-fold to 20-fold greater risk for puerperal infection than patients having vaginal delivery.

Patients having nonelective cesarean delivery (i.e., in labor with or without membrane rupture) are at more risk than patients having electively scheduled procedures. Particularly among indigent populations, the risks in this subgroup have been reported as 45% to 85%. Labor, membrane rupture, and vaginal examination increase postpartum infection, probably because they allow ascent of bacteria into the amniotic cavity before surgery.

Since the early 1970s, more than 30 randomized placebo-controlled trials have been reported on the use of prophylactic antibiotics representative in cesarean section (2,3). In one analysis, prophylactic antibiotics were found to decrease the overall rate of “serious infection” in patients undergoing cesarean section (emergency and elective combined) dramatically and significantly (typical odds ratio [OR], 0.24; 95% confidence interval [CI], 0.18–32) (2). Prophylactic antibiotics have been shown to have profound and consistent effects in reducing endometritis (typical OR, 0.25; 95% CI, 0.22–0.29) and wound infection (typical OR, 0.35; 95% CI, 0.28–0.44). Compared with placebo, both broad-spectrum penicillins and cephalosporins are highly effective (typical ORs, 0.33 and 0.31, respectively), whereas metronidazole (in five studies) showed no significant decrease (typical OR 0.72; 95% CI, 0.48–1.08).

Several studies have compared one antibiotic with another. There were no statistically significant differences in infection rates, but there were relatively few patients in these studies, and the absolute differences in infection rates were small (3% to 8%). Canadian investigators compared cefoxitin with cefazolin in nonelective cesarean sections and found no significant differences in rate of genital tract infection or in hospital stay (4). When the efficacy of broad-spectrum penicillins has been compared directly with that of cephalosporins, there has been no significant difference (typical OR, 0.89; 95% CI, 0.60–1.32) (2).

Studies comparing administration of the prophylaxis before versus after cord clamping have shown similar effectiveness (5,6).

Single-dose prophylaxis has been compared with multiple doses. Several individual studies have found equivalent efficacy between one dose and two or three doses of antibiotic for prophylaxis. In an analysis of nine studies comparing single and multiple doses, postoperative febrile morbidity was more common with single-dose prophylaxis (typical OR, 1.36; 95% CI, 0.95–1.95) (2), but the CI includes 1.0. Hemsell (3) noted that cesarean section after prolonged rupture of the membranes, presumptively associated with a large intrauterine inoculum, “may be the one procedure for which single-dose prophylaxis is not so effective as two doses

administered at an interval shorter than the 4 to 6 hours." The recent educational bulletin from the American College of Obstetricians and Gynecologists concluded that single-dose prophylaxis usually is sufficient. We support this position and would reserve two- or three-dose courses of prophylaxis for selected cases such as those with ruptured membranes for more than 12 hours, as noted by Hemsell (6).

As an alternative to parenteral administration of prophylactic antibiotics, there was a flurry of interest in intraoperative irrigation of the uterus and peritoneal cavity with antibiotic-containing solution. Publications 15 to 20 years ago established that this route is often equivalent to, but in some cases was less effective than, intravenous prophylaxis. Over the last 15 years, interest in this approach has waned (7,8,9 and 10).

Use of prophylaxis routinely (including in "low-risk" patients) remains controversial. The Oxford group concluded that giving antibiotics routinely at cesarean section would reduce costs by between £1,300 and £3,900 per 100 cesarean deliveries (at 1988 British prices), based on a literature review (11). In the United States, Ehrenkranz et al. (12) performed prospective and retrospective studies of women at low risk (defined as those having a scheduled procedure without an urgent indication, with any duration of ruptured membranes being 12 hours or less, and among patients in community hospitals). Absence of antibiotic prophylaxis was associated with endometritis ($p < 0.013$) or endometritis with wound infection ($p < 0.01$). Without prophylaxis, such infections occurred in 3.7% (37 of 957) versus 0.9% (8 of 906) with prophylaxis. It was estimated that routine antibiotic prophylaxis in low-risk cesarean sections "could lead to an annual national savings of approximately $9 million" (12). On the other hand, Howie and Davey (13), in editorial for the Oxford group's report, noted that prophylactic antibiotics were "important but not always necessary." The editorialists noted that the Oxford group's claim must be tested in prospective trials and that there have been both direct adverse effects of prophylactic antibiotics and development of resistant bacteria. It is one thing to draw conclusions in a metaanalysis, but quite another to decide on an individual mother. Similarly, Hemsell (3) concluded that a woman with intact membranes, not in labor, undergoing electively scheduled cesarean section "probably does not require prophylaxis." The recent position of the American College of Obstetricians and Gynecologists (6) is that "prophylaxis is not recommended routinely in low-risk patients because of concerns about adverse side effects, bacteriologic shifts toward resistant organisms, and relaxation of standard infection control measures and proper operative technique. We agree with these latter philosophies.

Untoward effects such as changes in flora and direct toxic reactions may accompany the use of antibiotics for prophylaxis (14). Systematic investigations have detected significant changes in antimicrobial flora after prophylactic antibiotics (14). Overall, there were decreases in highly susceptible organisms and increases in enterococci and Enterobacteriaceae organisms. Although many of the Enterobacteriaceae organisms were susceptible to the prophylactic agent, some isolates of *Pseudomonas* sp also appeared. In these cases, the bacterial changes were without consequence. Recently Newton and Wallace (15) reported the results of prophylactic antibiotics on endometrial flora in women with postcesarean endometritis. Patients who received cefazolin prophylaxis had a significant increase in enterococci ($p < 0.015$) and a significant decrease in *Proteus* sp ($p < 0.05$) when samples were taken from the endometrium by a sheathed aspiration technique at the time of endometritis. In contrast, patients who received ampicillin prophylaxis had a

significant increase in *Mycoplasma* species ($p < 0.5$), *Klebsiella pneumoniae* ($p < 0.0001$), *Escherichia coli* ($p = 0.04$), and any aerobic Gram-negative rod ($p = 0.003$). Ampicillin prophylaxis was associated with a decrease in *Prevotella bivia* (formerly *Bacteroides bivius*) ($p < 0.05$) and any anaerobic isolates ($p < 0.01$). Patients who received cephalosporin prophylaxis, followed by a cephalosporin for treatment, had significantly more wound infections than those who received other prophylaxis treatment combinations (19% vs. 16%; $p < 0.01$). Considerable evidence shows that antibiotic use for prophylaxis alters endometrial flora and has the potential to influence subsequent response rates to therapy (15). In patients who develop infection after prophylaxis, it is essential to obtain appropriate cultures to guide antibiotic therapy. Further, the antibiotic use for prophylaxis should not be used to treat a subsequent infection when one develops. In addition, extended-spectrum antibiotics should not be used for prophylaxis but should be reserved for treatment (6). Knowledge of the shifts in genital tract flora precipitated by antibiotic prophylaxis should considered when selecting antibiotics to be used for therapy of postprophylaxis endometritis.

Direct toxic effects are unlikely. No serious allergic or toxic reactions were noted among 1,443 patients receiving prophylaxis in 26 studies (5). Less serious reactions such as rash were reported on occasion. However, several cases of fatal anaphylactic reaction to prophylactic antibiotics were reported in orthopedic patients (16), and two cases of fatal pseudomembranous enterocolitis have been attributed to a combination of prophylactic therapeutic antibiotics (17). More recently, pseudomembranous colitis has been reported in 15 women having short-course prophylaxis (18,19 and 20). One case followed cefazolin prophylaxis; the other 14 followed cefoxitin prophylaxis. Block et al. (18) found *Clostridium difficile*–associated colitis to be significantly more common after cefoxitin (9 of 162) than after other antibiotics (0 of 8; $p = 0.02$). For patients who have documented immediate hypersensitivity reactions to penicillin, antibiotic choices for prophylaxis are limited. In such cases, cephalosporins are contraindicated, as are all penicillin-type antibiotics. One recommendation is for the use of single-dose clindamycin (900 mg), perhaps with a single dose of gentamicin (1.5 to 2.0 mg/kg) (6). Vancomycin may be used for prophylaxis of cesarean section endometritis in patients with an immediate hypersensitivity reaction to penicillin (Box 24.1).

Box 24.1. Recommendations for Use Of Prophylactic Antibiotics in Cesarean Section

1. Antibiotic prophylaxis is recommended for women undergoing nonelective cesarean section because such antibiotic use reduces the risk of endometritis and wound infections. Use of prophylaxis in this setting appears to be cost-effective.
2. Prophylaxis is not recommended routinely in low-risk patients such as those with documented low infection rates after undergoing an electively scheduled cesarean section.
3. Preferred antibiotics include a first-generation cephalosporin such as cefazolin (1 g intravenously) or ampicillin (1 to 2 g intravenously). Newer extended-spectrum cephalosporins or penicillins are no more effective and add cost to the prophylaxis.
4. Single-dose prophylaxis is usually sufficient, but in selected circumstances such as cesarean section after prolonged rupture of the membranes (e.g., 12 hours), a regimen of two- or three-dose prophylaxis is supported. Current information suggests that additional intraoperative doses of an antibiotic for prophylaxis should be given at intervals of one or two times the half-life of the antibiotic to maintain adequate levels of the antibiotic throughout the surgical procedure. Half-lives of representative antibiotics (in patients with normal renal function) are as follows: for cefazolin, 1.8 hours; cefoxitin, 60 minutes; cefotetan, 4 hours; and clindamycin, 3 hours (1).
5. The antibiotic used for prophylaxis should be initiated immediately after cord clamping (unless the rationale is to prevent group B streptococcal perinatal infection). This timing of antibiotic prophylaxis is equally effective as regimens beginning prophylaxis before cord clamping, and this regimen avoids direct and indirect adverse effects on the newborn.
6. Antibiotics used for prophylaxis dramatically shift upper genital tract flora. Extended-spectrum antibiotics should not be used for prophylaxis. For patients who develop genital tract infection after prophylaxis, a culture for aerobes should be obtained to direct subsequent antibiotic therapy and to direct antibiotic policies in a given hospital. Antibiotics used for prophylaxis should not be used for therapy in the same patient. If a cephalosporin was used for prophylaxis, a treatment regimen active against enterococci should be considered. If ampicillin is used for prophylaxis, a treatment regimen active against *Klebsiella* organisms should be considered.
7. For patients who have immediate hypersensitivity reactions to penicillin, antibiotics for prophylaxis are limited. One recommendation is to use a single dose of clindamycin (900 mg), either with or without gentamicin in a dose of 1.5 to 2.0 mg/kg. If there is also a contraindication to clindamycin, vancomycin may be used. The Infectious Diseases Society of America recommends vancomycin for prophylaxis instead of cefazolin or alternative cephalosporins in patients who are allergic to cephalosporins. Further, the recommendation is that because vancomycin provides no activity against Gram-negative bacilli, another antibiotic with Gram-negative activity should be added to this regimen. Such an alternative includes aztreonam or aminoglycoside (1).

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8. Direct adverse effects of antibiotics used for prophylaxis have been reported, including life-threatening complications such as anaphylaxis and pseudomembranous colitis.
9. Use of prophylactic antibiotics must not result in relaxation of standard infection control measures.
10. Antibiotics administered by irrigation are not more effective than those given by intravenous injection.

A common concern about widespread use of prophylaxis is a dangerous relaxation of standard infection control measures. Clearly, hand-washing, appropriate isolation techniques, proper disposal of infected materials and dressings, and changing of soiled scrub suits remain important elements in the control of infections and cannot be replaced capriciously by antibiotic prophylaxis. Recommendations for use of antibiotics in patients undergoing cesarean section are provided in Table 24.1 and Box 24.1.

Procedure	Efficacy
Cesarean delivery	Typical odds ratio, 0.2 to 0.3 (2)
Vaginal hysterectomy	Estimated 82% of infections are prevented (19)
Abdominal hysterectomy	Estimated 49% of infections are prevented (19)
Therapeutic abortion	Estimated up to half of infections are prevented (24)
Intrauterine device insertion	Efficacy of prophylaxis not established (27)
Hysterosalpingography	Efficacy of prophylaxis not established (23)
Laparoscopy, ovarian, cystectomy, and other clean procedures	Prophylaxis not recommended (23)

TABLE 24.1. SUMMARY OF EFFICACY OF ANTIBIOTIC PROPHYLAXIS IN OBSTETRIC AND GYNECOLOGIC PROCEDURES TO PREVENT PELVIC INFECTION

Other Obstetric Considerations

For a full discussion of the use of prophylactic antibiotics for prevention of group B streptococcal perinatal infection and in premature rupture of the membranes, see Chapter 3 (Group B Streptococci) and Chapter 19 (Subclinical Infection as a Cause of Premature Labor), respectively.

USES IN GYNECOLOGY

Studies in gynecologic patients have focused mainly on vaginal and abdominal hysterectomy, but there have been additional studies of other procedures. Table 24.1 summarizes the efficacy of antibiotic prophylaxis.

Vaginal Hysterectomy

The risk of postoperative infection in patients undergoing vaginal hysterectomy varies widely. In the Professional Activities Study, 38% of 3,500 patients having vaginal hysterectomy had fever of more than 101°F (21). Premenopausal women are at high risk for infection after vaginal hysterectomy. Women with a hysterectomy within 24 to 72 hours after cervical conization also encounter a higher rate of postoperative infection (22). Among double-blind placebo-controlled studies, there is a consistent finding of decreased postoperative infection (most studies showing statistically significant differences) with use of antibiotic prophylaxis. Polk (23) calculated an overall preventive fraction of 82% in 11 studies of short-course prophylaxis. Numerous studies have compared different antibiotics for prophylaxis in patients with vaginal or abdominal hysterectomy. These studies have compared short courses (single dose to 12 hours vs. long courses [48 to 72 hours]), different antibiotics in the same or different dosing regimens, the same antibiotic in differing regimens, and antibiotics versus suction drainage. Few of these studies showed any significant differences in rates of postoperative infection. The findings of these well-designed studies are remarkably consistent in showing statistically significant and clinically impressive decreases in postoperative infection.

Abdominal Hysterectomy

Infection after abdominal hysterectomy appears to be less frequent than infection after vaginal hysterectomy, possibly due to less contamination from the vagina (21). In a metaanalysis, “serious infections” (including abdominal wound infection, pelvic cellulitis, pelvic abscess, vaginal cuff abscess, and septicemia) developed in 21% (373 of 1,768) of patients undergoing abdominal hysterectomy without prophylaxis (24).

Of numerous double-blind placebo-controlled studies of antibiotic prophylaxis in patients who underwent abdominal hysterectomy, few individual studies show a significant decrease in postoperative infection, but nearly all show an absolute decrease. Polk (23) calculated that in studies using short-course prophylaxis, 49% of postoperative infections are prevented. A recent metaanalysis of rigorously conducted trials found a significant reduction in “serious postoperative infection” (as defined previously) among patients who received antibiotic prophylaxis compared with those who did not (9.0% [166 of 1,836] vs. 21.1% [373 of 1,768]; $p = 0.00001$). Individual antibiotics with demonstrated significant decreases were cefazolin ($p = 0.0002$), metronidazole ($p = 0.015$), and tinidazole (a drug similar to metronidazole, $p = 0.034$) (24). As for vaginal hysterectomy, many studies have compared different regimens, with little overall difference among regimens. Thus, broader spectrum, more expensive antibiotics for prophylaxis are no more effective than older antibiotics such as cefazolin. Further, because single-dose cefazolin prophylaxis appears to be equivalent to three-dose regimens, we do not recommend use of newer longer acting agents for prophylaxis. As pointed out by Shapiro et al. (25), the benefit-cost ratio is decreased considerably by the use of the more expensive antibiotics for prophylaxis. Under special conditions, such as long cases or those with high blood loss, second doses of the prophylactic antibiotic may be beneficial.

Adverse Effects of Prophylaxis in Hysterectomy

Among patients receiving cephalosporin prophylaxis for abdominal or vaginal hysterectomy, there was a shift toward more resistant isolates. Changes in flora have also been noted in patients who received short-course prophylaxis for hysterectomy, but these changes were similar to those in patients who received placebo. Other adverse effects, including rashes and abnormalities in chemistry or hematology studies, have been reported infrequently.

Alternatives to Prophylaxis in Hysterectomy

Significant decreases in postoperative infections had been demonstrated by the use of suction drainage through a T-tube catheter (26). Later studies, however, showed prophylactic antibiotics to be superior to T-tube suction drains (27).

Patients with an abnormal vaginal flora are more likely to have postoperative infection. Thus, if a condition such as bacterial vaginosis is detected preoperatively, it should be treated either topically or orally before the patient is admitted to the hospital, whether the condition is symptomatic or asymptomatic (28).

Recommendations for Hysterectomy

Please see Box 24.2.

Therapeutic Abortion

The risk of upper genital tract infection after therapeutic abortion ranges from 5% to 20% (29). Retrospective reports from the United States had suggested that the incidence might be less than 1%. It is recognized that there were long-term sequelae of postabortal infection including chronic pelvic pain and infertility. It may be argued that because most women undergoing suction abortion in the United States are young, unmarried, and nulliparous, there is an urgency in preventing upper genital tract infections, which can adversely effect fertility. Problems with earlier studies of prophylactic antibiotics for therapeutic abortions included the rather vague definition of infection. It was noteworthy that nearly all of the infections were minor or minimal (30). Additional problems were that side effects from the antibiotics were common, particularly when doxycycline was used for prophylaxis. For example, vomiting developed in 18% of patients (31). More recent views support universal prophylaxis for therapeutic abortion (28,29). Organisms most likely to cause postabortal endometritis include the sexually transmitted organisms *Neisseria gonorrhoeae* and *Chlamydia trachomatis,* as well as the array of aerobic and anaerobic organisms found in the pelvis (28). Accordingly, regimens to be used for prophylaxis include doxycycline, ofloxacin, and ceftriaxone (28). The course of prophylaxis should be short and may be given orally, such as 200 mg of doxycycline before and 12 hours after the procedure. Erythromycin orally and metronidazole orally have also been used (29). A recent metaanalysis by Sawaya et al. (29) assessed 12 studies and reported an overall summary relative risk for developing postabortal upper genital tract infection in women receiving antibiotic prophylaxis of 0.58 (95% CI, 0.47–0.72) compared with women receiving placebo. In all subgroups of women, there was a significant protective effect. In high-risk women, such as those with a history of pelvic

inflammatory disease, there was a summary relative risk of 0.56 (95% CI, 0.37–0.84). Women who had positive culture results for chlamydiae at the time of abortion had a summary relative risk of 0.38 (95% CI, 0.15–0.92). Even in women with no risk factors, the relative risk was protective at 0.65 (95% CI, 0.47–0.90). Thus, it is recommended that routine perioperative antibiotics be used in patients having abortion in the United States to prevent approximately half of the cases of postprocedural infection.

Box 2. Recommendations for Antibiotic Prophylaxis with Hysterectomy

1. Short-course prophylaxis significantly reduces the risk of pelvic infection in patients undergoing vaginal or abdominal hysterectomy. Antibiotic prophylaxis is likely to be more effective in lowering infection after vaginal hysterectomy than after abdominal hysterectomy.
2. Antibiotic selection for prophylaxis for abdominal hysterectomy includes primarily first-generation cephalosporins such as cefazolin (1). An alternative antibiotic to be used is ampicillin (28). Some experts also recommend second- and third-generation cephalosporins such as cefoxitin, cefotetan, or ceftizoxime and broader spectrum penicillin such as mezlocillin and piperacillin (28).
3. As with cesarean section, prophylactic antibiotics should be given as a single dose for most procedures. If the operation lasts more than approximately 3 hours, or if the blood loss exceeds 1,500 mL, a second dose may be beneficial (28).
4. Shifts in bacteria undoubtedly occur after antibiotic prophylaxis, as in cesarean section. Accordingly, recommendations for performing cultures and for therapeutic strategies should be the same as recommended under cesarean sections. Specifically, cephalosporins are likely to lead to emergence of resistant enterococci, resistant *E. coli,* and *Bacteroides fragilis*; penicillins tend to select for resistant Gram-negative bacteria.
5. It is important to monitor infection rates within each hospital to assess changes in effectiveness of an antibiotic regimen (28).
6. In patients who are allergic to penicillins or cephalosporins, alternative antibiotics for prophylaxis include clindamycin, doxycycline, metronidazole (28), or in special cases, vancomycin (1).
7. Again, as with cesarean section, antibiotic prophylaxis may cause direct adverse effects.
8. As with cesarean section, good intraoperative technique remains essential.

Gynecologic Oncology

Antibiotic prophylaxis is widely used in major surgery for gynecologic cancer, but randomized trials have less extensive data than in hysterectomy for benign indications (32,33,34,35 and 36). Current data suggest that prophylaxis is effective for radical surgery but that individual determinations of the need for prophylaxis should be made. When used in such cases, recommendations are the same as

those for other hysterectomy procedures. Overall, it is likely that infections are decreased, because there is a substantial likelihood of a beta error in individual studies because of the small sample size.

OTHER GYNECOLOGIC PROCEDURES

After hysterosalpingography, the risk of pelvic inflammatory disease is 0.3% to 3.4% (3). Tests for sexually transmitted diseases should be performed before the procedure, and appropriate treatment given. There are no randomized blind trials, and indeed they would be difficult to complete given the low overall infection rate. Nevertheless, prophylaxis has been advised for decades presumably based on the observation that bacteria are commonly carried with the dye into the endometrial cavity, through the fallopian tubes and into the peritoneum (28).

Before intrauterine device (IUD) insertion, tests for sexually transmitted diseases should be performed and appropriate treatment given. In a randomized trial of doxycycline versus placebo, there was no significant reduction in postinsertion infection (1.9% vs. 1.3%; $p = 0.17$), but those with prophylaxis had fewer unscheduled postinsertion visits (3). An additional randomized controlled trial was recently reported among nearly 2,000 patients taking either azithromycin (500 mg) or placebo 1 hour before insertion of a copper T-shaped IUD. There was no significant difference in the rate of IUD removal for any reason (other than partial expulsion) (3.8% in the antibiotic group and 3.4% in the placebo group). The two groups had a similar number of subsequent visits, and in the 90 days after IUD insertion, only one woman from each group had a diagnosis of salpingitis. Thus, the risk of upper genital tract infection after IUD insertion was negligible with or without the administration of prophylactic antibiotics (37). One report indicated that changing the time of insertion from during menses to within 2 days of predicted ovulation eliminated "inflammatory-type reactions." Overall, prophylactic antibiotics are not recommended for routine use with IUD insertion.

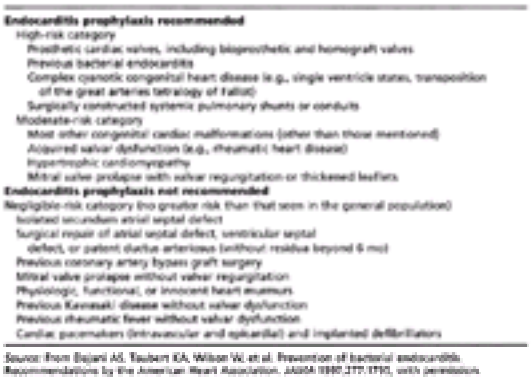
For infertility surgery, prophylactic antibiotics are commonly used, but there are no prospective randomized trials. It is reasonable to use a single dose of cefazolin for tubal reconstructive surgery and a single oral dose of doxycycline for laparoscopy with hydrotubation (3). For clean procedures such as myomectomy, ovarian cystectomy, and resection of endometriosis, prophylaxis is not recommended (3). Bacteriuria was not decreased after combined urodynamics and cystourethroscopy among women taking a 1-day course of nitrofurantoin versus placebo (38). Similarly, among women having curettage for incomplete abortion, prophylactic doxycycline did not decrease the rate of postoperative febrile morbidity (39).

PROPHYLAXIS OF BACTERIAL ENDOCARDITIS

Bacteremia develops in perhaps 1% to 5% of women during uncomplicated delivery and in an undetermined percentage of women undergoing pelvic surgery. Bacteremia has been found in 3% to 20% of obstetric patients with infection. In 1997, the American Heart Association issued revised guidelines for antibiotic prophylaxis to prevent endocarditis (40). These recommendations included a number of changes. These include stratification of cardiac conditions into high-, moderate-, and negligible-risk groups based on the potential outcome if endocarditis develops; identification of procedures that may cause bacteremia and for which prophylaxis is

recommended; development of an algorithm to more clearly define when prophylaxis is recommended in patients with mitral valve prolapse; and simplification of a prophylactic regimen for patients with gastrointestinal and genitourinary procedures.

Cardiac conditions for which endocarditis prophylaxis is either recommended or not recommended appear in Table 24.2. A clinical approach to determine the need for prophylaxis in patients with suspected mitral valve prolapse was provided. Overall, if there is a murmur of mitral regurgitation, then prophylaxis is indicated. If the presence or absence of mitral regurgitation is either not determined or not known, and if confirmation is not available, prophylaxis is recommended if there is an immediate need for the procedure. Otherwise, the patient should be referred for evaluation and a determination of the need for prophylaxis should be based on detection of the murmur by a cardiologist, by echocardiography or by Doppler flow studies.



Endocarditis prophylaxis recommended
- High-risk category
  - Prosthetic cardiac valves, including bioprosthetic and homograft valves
  - Previous bacterial endocarditis
  - Complex cyanotic congenital heart disease (e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot)
  - Surgically constructed systemic pulmonary shunts or conduits
- Moderate-risk category
  - Most other congenital cardiac malformations (other than those mentioned)
  - Acquired valvar dysfunction (e.g., rheumatic heart disease)
  - Hypertrophic cardiomyopathy
  - Mitral valve prolapse with valvar regurgitation or thickened leaflets

Endocarditis prophylaxis not recommended

Negligible-risk category (no greater risk than that seen in the general population)
- Isolated secundum atrial septal defect
- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 mo)
- Previous coronary artery bypass graft surgery
- Mitral valve prolapse without valvar regurgitation
- Physiologic, functional, or innocent heart murmurs
- Previous Kawasaki disease without valvar dysfunction
- Previous rheumatic fever without valvar dysfunction
- Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

Source: From Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277:1794; with permission.

TABLE 24.2. CARDIAC CONDITIONS ASSOCIATED WITH ENDOCARDITIS

Recommendations

The revised recommendations show that endocarditis prophylaxis is recommended with cystoscopy and with urethral dilation. However, endocarditis prophylaxis is not recommended routinely with vaginal hysterectomy, vaginal delivery, cesarean section, or with uninfected tissues with dilation and curettage, therapeutic abortion, sterilization procedures, or insertion or removal of IUDs. However, the committee continues to note that prophylaxis is optional for high-risk patients (Table 24.2) undergoing vaginal hysterectomy or vaginal delivery. Antibiotic therapy is, of course, indicated in the treatment of patients with infected products of conception undergoing dilation and curettage or for the removal of an IUD in the presence of pelvic inflammatory disease (Table 24.3).

Endocarditis prophylaxis recommended
Cystoscopy
Urethral dilation
Endocarditis prophylaxis not recommended
Vaginal hysterectomy
Vaginal delivery
Cesarean section
In uninfected tissue:
Urethral catheterization
Uterine dilation and curettage
Therapeutic abortion
Sterilization procedures
Insertion or removal of intrauterine devices

Source: From Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277:1794–1801, with permission.

TABLE 24.3. OBSTETRIC GYNECOLOGIC PROCEDURES AND ENDOCARDITIS PROPHYLAXIS

Regimen

Endocarditis prophylaxis during pelvic procedures is directed primarily against enterococci (e.g., *Streptococcus faecalis*). Although Gram-negative organisms are among the most common microbes causing bacteremia in this population, these organisms rarely cause endocarditis. Table 24.4 lists the recommended regimens.

Situation	Agents[a]	Regimen[b]
High-risk patients	Ampicillin plus gentamicin	Adults: ampicillin 2.0 g intramuscularly (i.m.) or intravenously (i.v.) plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure; 6 hr later, ampicillin 1 g i.m. or i.v. or amoxicillin 1 g orally Children: ampicillin 50 mg/kg i.m. or i.v. (not to exceed 2.0 g) plus gentamicin 1.5 mg/kg within 30 min of starting the procedure; 6 hr later, ampicillin 25 mg/kg i.m. or i.v. or amoxicillin 25 mg/kg orally
High-risk patients allergic to ampicillin/amoxicillin	Vancomycin plus gentamicin	Adults: vancomycin 1.0 g i.v. over 1–2 hr plus gentamicin 1.5 mg/kg i.m. or i.v. (not to exceed 120 mg); complete injection/infusion within 30 min of starting the procedure Children: vancomycin 20 mg/kg i.v. over 1–2 hr plus gentamicin 1.5 mg/kg i.m. or i.v.; complete injection/infusion within 30 min of starting the procedure
Moderate-risk patients	Amoxicillin or ampicillin	Adults: amoxicillin 2.0 g orally 1 hr before procedure, or ampicillin 2.0 g i.m. or i.v. within 30 min of starting the procedure Children: amoxicillin 50 mg/kg orally 1 hr before procedure, or ampicillin 50 mg/kg i.m. or i.v. within 30 min of starting the procedure
Moderate-risk patients allergic to ampicillin/amoxicillin	Vancomycin	Adults: vancomycin 1.0 g i.v. over 1–2 hr; complete infusion within 30 min of starting the procedure Children: vancomycin 20 mg/kg i.v. over 1–2 hr; complete infusion within 30 min of starting the procedure

[a] Total children's dose should not exceed adult dose.
[b] No second dose of vancomycin or gentamicin is recommended.
Source: From Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277:1794, with permission.

TABLE 24.4. PROPHYLACTIC REGIMEN FOR GENITOURINARY PROCEDURES

In patients with significantly compromised renal function, it may be necessary to modify the dose of antibiotics used.

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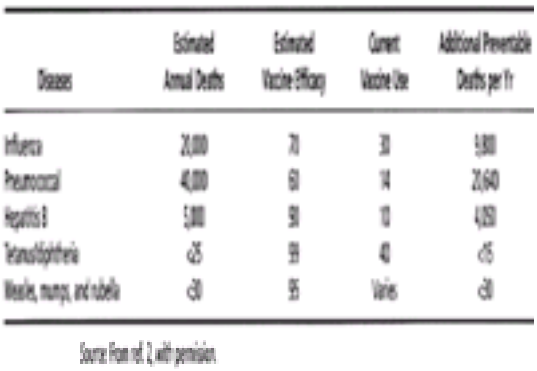
25

IMMUNIZATION

Immunization of adults has not received the same high priority as immunization of children (1,2,3 and 4). Paradoxically, in the United States, deaths from vaccine-preventable diseases occur predominantly in adults, with an estimated 50,000 to 70,000 adults dying each year from such diseases (1,2,3,4 and 5). Predominantly, mortality is due to pneumonococcal infection, influenza, and hepatitis B (Table 25.1). In fact, vaccine-preventable deaths exceed those resulting from automobile accidents or acquired immunodeficiency syndrome (AIDS) (2,3 and 4). Factors that contribute to the poor record of adult immunization include (a) concerns about safety and efficacy of vaccines among the general public and health care workers; (b) uncertainty about specific recommendations; (c) liability concerns; (d) inadequate reimbursement for immunizations; (e) a poorly informed public; and (f) an independently developed system for immunization of adults (2,4,5).



Disease	Estimated Annual Deaths	Estimated Vaccine Efficacy	Current Vaccine Use	Additional Preventable Deaths per Yr
Influenza	20,000	70	30	9,800
Pneumococcal	40,000	60	14	20,640
Hepatitis B	5,000	90	10	4,050
Tetanus/diphtheria	<25	99	40	<15
Measles, mumps, and rubella	<20	95	Varies	<20

Source: From ref. 2, with permission.

TABLE 25.1. ESTIMATES OF THE EFFECT OF FULL USE OF THE VACCINES ADVOCATED FOR ADULTS

Of the more than 50 biologic products available in the United States for immunization, seven major vaccines are designed for routine use in adults (Table 25.2) (1,2,3,4 and 5). It is important that obstetrician-gynecologists be involved in providing immunization of adults. Unfortunately, vaccination of adult patients has been inadequately addressed by obstetrician-gynecologists and other primary care

providers (6,7). For example, the American College of Physicians' Task Force on Immunizations has recommended that age 50 be established as the time to review preventive health measures including an emphasis on risk factors that identify patients in need of pneumococcal and hepatitis B vaccines and initiation of annual influenza immunization (8). This chapter discusses the general principles of immunization, specific details for use of these seven vaccines, and special circumstances related to immunizations such as pregnancy, occupational exposure, travel, postexposure immunizations, and immunocompromised states.

Diphtheria toxoid, tetanus toxoid
Measles, mumps, and rubella
Hepatitis B virus
Influenza virus
Polyvalent pneumococcal polysaccharides
Varicella vaccine
Hepatitis A vaccine

TABLE 25.2. MAJOR VACCINES RECOMMENDED FOR ROUTINE USE IN ADULTS

General Principles Of Immunization

Immunization is the process by which either immunity is artificially induced or protection from disease is provided (9). Immunization can be active or passive. Active immunization induces the body to develop defenses against infection; it is accomplished with vaccines or toxoids that stimulate the immune system to produce antibodies, cell-mediated immunity, or both, which in turn protects against an infectious disease (9). Passive immunization is a process that provides temporary protection against an infectious agent by administration of exogenously produced antibody (9). The most common methods of passive immunization are transplacental passage of maternal antibodies to the fetus and the use of immunoglobulin (Ig) to prevent specific infectious diseases (9). Immunizing agents include the following: (a) vaccine, a suspension of attenuated live or killed microorganisms or fractions thereof administered to induce immunity; (b) toxoid, a modified bacterial toxin that has been rendered nontoxic but is still capable of producing antitoxin; (c) Ig, a solution containing antibody from human blood that can provide passive immunization against certain infections (e.g., measles and hepatitis A) or routine protection of immunodeficient patients; and (d) specific Ig, special preparations obtained from donor pools with a high antibody content against a specific disease (e.g., hepatitis B immune globulin [HBIG] and varicella-zoster immune globulin [VZIG]) (9).

Historical Perspective

Jenner (10) undertook the first scientific attempt to control an infectious disease through deliberate inoculation (11). In 1796, he demonstrated that milkmaids who had contacted cowpox (vaccinia) were immune to smallpox. Subsequently, Jenner inoculated susceptible persons with vesicular fluid from cowpox lesions and induced protection against smallpox (9,10 and 11). This commenced the era of immunization, whose impact on reducing mortality and augmenting population growth is surpassed only by improved sanitation and safe water (11). In the 200 years since Jenner, the introduction of vaccines has controlled the following ten major infectious diseases in at least some areas of the world: smallpox, diphtheria, tetanus, pertussis, yellow fever, poliomyelitis, measles, mumps, rubella, and *Haemophilus influenzae* type B disease. Vaccination has resulted in the global eradication of smallpox (12) and the elimination of poliomyelitis caused by wild virus in the United States (9,13,14). Great progress has been made worldwide toward the goal of polio eradication (14,15). Recently, the Centers for Disease Control and Prevention (CDC) reported that the western Pacific region of the World Health Organization (WHO) (e.g., Australia, China, Japan, Korea, Philippines, and New Zealand) as of October 2000 has been certified as free of indigenous wild poliovirus transmission (16). No cases of polio due to wild virus have been reported in the Western Hemisphere since 1991 (14) and no new indigenous cases have been detected in the European region of the WHO since 1998 (16,17). The WHO recently suggested that global circulation of poliovirus may be interrupted by 2002 (17).

In addition to the eradication of smallpox and poliomyelitis in the United States, a dramatic reduction in the incidence rates of other diseases has occurred with the widespread use of vaccines (Table 25.3) (9). There has been a more than 90% reduction in measles, diphtheria, and rubella in developed countries (18). Although *H. influenzae* type B (Hib) vaccine has only recently become available on a widespread basis, it has markedly reduced the incidence of this disease in many developed countries (9,19). With more widespread availability, hepatitis B vaccine use in infants should have an impact on disease reduction comparable to that of the other childhood vaccines (9). Similarly, major advances have been made by vaccines against influenza and pneumococcal infection (11).

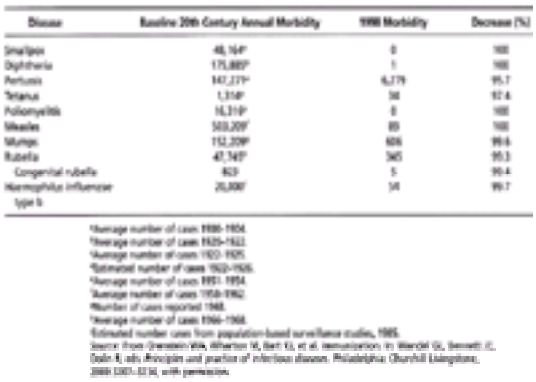


TABLE 25.3. BASELINE 20th CENTURY ANNUAL MORBIDITY AND 1998 MORBIDITY FROM NINE DISEASES WITH VACCINES RECOMMENDED BEFORE 1990 FOR UNIVERSAL USE IN CHILDREN—UNITED STATES

Safety and Efficacy of Vaccines

Although modern vaccines are very effective and safe, all vaccines are associated with some adverse effects and all vaccines are not 100% effective (8). Despite the demonstrated high efficacy of vaccines, controversy has arisen over adverse effects attributed to vaccine use (8). In response to these concerns, the Institute of Medicine (IOM) undertook an assessment of the available data for 9 of the 11 vaccines universally recommended for children and the serious adverse events reported to be associated with these vaccines (20,21 and 22). In most cases, there was insufficient evidence to establish causation (9). Table 25.4 summarizes the IOM findings for adverse events in which data were available to reach a conclusion. Subsequently, the IOM findings were reviewed by the Advisory Committee on Immunization Practices (ACIP), which assessed newer data related to Guillain-Barré syndrome. Based on these newer data, the ACIP did not confirm a causal relationship between Guillain-Barré syndrome and either oral poliovirus (OPV) vaccine, diphtheria toxoid, tetanus toxoid, and pertussis (DTP) vaccine, or tetanus toxoid (T) vaccine (23,24). In addition, recent studies failed to substantiate an increased risk for chronic arthritis among women inoculated with RA27/3 (rubella virus) vaccine (25,26).

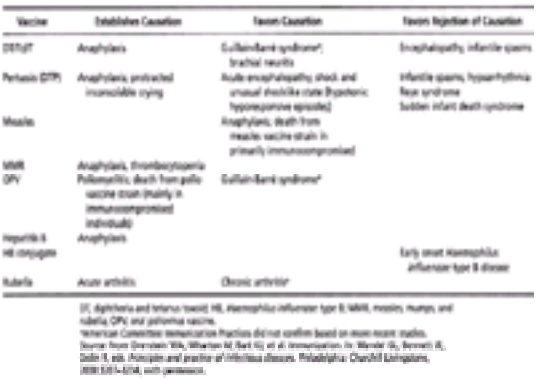


TABLE 25.4. SUMMARY OF INSTITUTE OF MEDICINE FINDINGS ON THE RELATIONSHIP OF ADVERSE EVENTS TO INDIVIDUAL VACCINES

In the case of pregnancy, there is no direct evidence of risk to the fetus when pregnant women are inoculated with a particular vaccine (9). However, most live virus vaccines result in viremia, which can lead to infection of the fetus (8). Thus, live virus vaccines are not administered to pregnant women except in special circumstances (9,27).

Immunization Programs for Adults

In the United States, recommendations for vaccine use are developed by three bodies: (a) The ACIP of the CDC develops recommendations oriented toward the public health arena (28,29); (b) the Committee on Infectious Diseases of the

American Academy of Pediatrics (AAP) (Red Book) develops recommendations for use in private pediatric practice (30); and (c) the Task Force on Adult Immunization of the American College of Physicians and the Infectious Diseases Society of America develop recommendations for adults in the private sector (8). Currently, the ACIP, AAP, and the American Academy of Family Physicians collaborate and issue a consensus schedule for childhood immunizations that is updated annually (28).

The immunization schedule recommended for adults is divided into three age-groups (Table 25.5) (8,29). In the 18- to 24-year-old age-group, it is recommended that (a) diphtheria and tetanus booster be given at age 16; (b) Measles, mumps, and rubella (MMR) vaccination with a second dose from kindergarten to college entry; (c) influenza virus vaccine given to high-risk groups and considered for all patients; and (d) varicella virus vaccine given to patients with no history of clinical varicella. Individuals in the 25- to 64-year-old age-group should receive (a) tetanus and diphtheria toxoids (Td) booster every 10 years or a single booster at age 50; (b) MMR vaccine for persons born during or after 1957; (c) influenza virus vaccine for all persons in this age-group is strongly recommended, particularly health care providers and others at increased risk for exposure or transmission; (d) pneumococcal vaccine for persons with risk factors for acquiring invasive pneumococcal disease; and (e) varicella virus vaccine in patients with no clinical history of varicella. For those 65 years of age or older, it is recommended that they receive influenza virus vaccine annually and pneumococcal vaccine every 6 years.

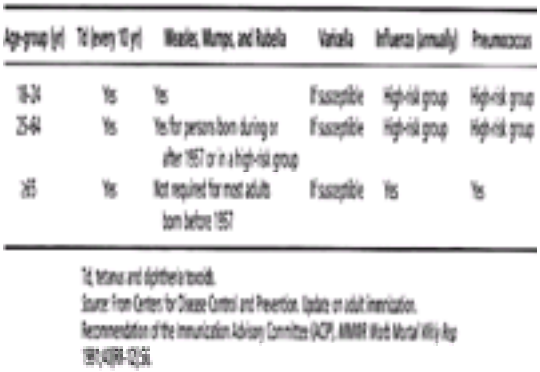


TABLE 25.5. OVERVIEW OF RECOMMENDED ROUTINE VACCINATIONS FOR ADULTS

Currently, five major types of vaccines are available: (a) live attenuated viruses or bacteria (e.g., cowpox, OPV, typhoid, cholera); (b) killed whole viruses (e.g., Salk poliovirus vaccine and influenza virus vaccine); (c) killed bacteria (e.g., pertussis, typhoid, and cholera); (d) purified component vaccines such as polysaccharide vaccines (e.g., pneumococcal and Hib vaccines) or toxins (e.g., tetanus toxoid and diphtheria toxoid); and (e) genetically engineered proteins produced by recombinant technology (e.g., hepatitis B vaccine). In the future, a sixth type, DNA vaccines, will be available that will provide direct inoculation with purified DNA. The advantages of DNA vaccines are that they stimulate both the hormonal and the cell-mediated arms of the immune system, they do not require new technology, they are more stable,

and they are less expensive. This technology will allow for rapid creation of new vaccines.

General Contraindications to Vaccines/Immune Therapy

As noted by Orenstein et al. (9), the decision to use a vaccine must take into account the risks of disease, the benefits of vaccination, and the risks associated with vaccination. There are several contraindications to vaccination that can be generalized to all vaccines: (a) previous anaphylactic reaction to the same vaccine; (b) previous anaphylactic reaction to a vaccine constituent; and (c) presence of moderate or severe illness, with or without a fever.

Although concern has been raised regarding the use of vaccines in pregnant and lactating women, the risks in pregnancy and lactation are primarily theoretical. In pregnancy, the benefit is greater than the risk when (a) the risk for disease exposure is high (e.g., travel to endemic areas); (b) infection would pose a special risk to pregnant women (e.g., influenza); and (c) vaccine is unlikely to cause harm. Breast-feeding is generally not a contraindication to vaccines or immune therapy. Killed and attenuated vaccines do not replicate. Although live virus vaccines (e.g., rubella virus vaccine) may replicate and be excreted in breast milk, the neonate is usually not infected and any infection is well tolerated.

From 1966 until recently, vaccination in pregnant women was discouraged and not recommended. The rationale for such an approach was not based on scientific data but occurred as a “knee-jerk” reaction to protect pregnant women and their fetuses. Vaccination in pregnant women to protect both mother and offspring was practiced extensively in the United States from 1957 to 1966 at a time when immunization with influenza virus and poliovirus vaccines was recommended during pregnancy. The safety of vaccination during pregnancy was demonstrated by the Collaborative Perinatal Project (31), which enrolled more than 50,000 pregnant women between 1959 and 1965 and evaluated more than 9,000 vaccine doses administered during the first 4 months of pregnancy. The vaccines most commonly used were inactivated poliovirus vaccines (18,342 women), live attenuated OPV vaccine (3,056 women), and influenza virus vaccine (2,291 women). These immunizing agents were not associated with the principal outcomes of the study. Based on extrapolation from the immunization rates in the project, an estimated 2 million doses of vaccine were given to pregnant women each year from 1959 to 1965. Moreover, the vaccines available currently are less “reactogenic,” more immunogenic, and better standardized.

A contraindication means that a vaccine should not be administered (32,33). On the other hand, a precaution identifies a situation in which a vaccine may be appropriate if after careful assessment of the benefit of vaccination is judged to outweigh the risk (32,33). As reviewed by Watson and Peter (32), the contraindications and precautions can be generic and applicable to all vaccines or they can be specific to a particular vaccine. The specific contraindications and precautions as recommended by the ACIP and AAP are discussed in the sections for each vaccine. Immunosuppression, as a result of either underlying disease or therapy, is a contraindication to use of most live virus or bacterial vaccines (32). Measles vaccination of persons infected with the human immunodeficiency virus (HIV) (not severely immunocompromised) is an exception (34). In a similar vein, live virus vaccines should not be administered to individuals who have received high doses of systemic corticosteroids for 14 days or more until 1 month or more after steroid

therapy was discontinued (35,36). Although most live virus vaccines, based on theoretical grounds, are contraindicated for pregnant women, the small theoretical risk associated with live virus vaccines in pregnant women may be far outweighed by the benefit of not contracting a disease with serious consequences for the mother and fetus (32).

Diphtheria And Tetanus Toxoid And Pertussis

Background

In the past, diphtheria was a major cause of morbidity and mortality, with death rates in the late 19th century averaging nearly 200 per 100,000 population annually and the proportion of total deaths attributable to diphtheria annually ranged from 3% to 10% (37). In that era, there were 50% more deaths from diphtheria than cancer. With the introduction of diptheria toxoid, the incidence of diphtheria fell dramatically, so from 1980 to 1995, only 41 cases of respiratory diphtheria were reported to the CDC (38). In 1998, only one case of diphtheria was reported in the United States (39).

Tetanus is caused by the bacterium *Clostridium tetani* and is unique among the vaccine-preventable diseases because it is not a communicable disease (40). Tetanus, despite the presence of a highly effective toxoid, remains a major public health problem worldwide, with an estimated 1 million deaths per year due to neonatal tetanus and an estimated 310,000 to 700,000 nonneonatal cases, resulting in 122,000 to 300,000 deaths annually in developing countries (40). On the other hand, there are approximately 2,000 cases and 1,000 deaths annuawith improved hygiene and childbirth practices and improvement in wound care.

Pertussis is caused by *Bordetella pertussis* and at one time was a major cause of morbidity and mortality in infants and children in the United States (39). From the time pertussis became a reportable disease (1920s) through the early 1940s, 115,000 to 270,000 cases of pertussis were reported each year in the United States, with 5,000 to 10,000 deaths annually (40). The availability and widespread use of pertussis vaccine in children led to a dramatic decrease in the incidence of pertussis, with 7,405 cases reported to the CDC in 1998 (39).

Indications

Diptheria and tetanus toxoids combined with acellular pertussis (DTaP) vaccine is the preferred vaccine and is recommended for all infants. The Td vaccine is recommended as a booster for all children aged 10 to 11 years with subsequent boosters recommended every 10 years (28). Use of whole-cell DTP remains an acceptable alternative.

Specific Contraindications and Complications

Severe reactions to the DT, tetanus and diptheria toxoids, or tetanus toxoid alone are unusual. As noted in Table 25.4, anaphylaxis has been established to result (rarely) from diphtheria and tetanus toxoids. The data favor a causative role of diphtheria and tetanus toxoids for brachial neuritis. Although initial data favored causation of Guillain-Barré syndrome (21), more recent assessments do not. The IOM found no evidence of causation for DT, tetanus and diphtheria, or tetanus toxoid alone for

encephalopathy or infantile spasms.

The pertussis vaccine given in combination with diphtheria and tetanus toxoids (i.e., the DTP vaccine) is felt to be causative for anaphylaxis (rare) and protracted inconsolable crying in infants (Table 25.4) (20,22). The IOM report favored a causative role of pertussis vaccine for acute encephalopathy and shock, as well as an unusual shocklike state characterized by hypotonia and unresponsiveness (20,22). No evidence implicates pertussis vaccine in infantile spasms, hypsarrhythmia, Reye syndrome, or sudden infant death syndrome (20,22). Whole-cell pertussis vaccines have been recognized for a long time as the vaccine associated with the greatest risk for adverse reactions—mostly minor but on occasion serious (41). Concern about the use of whole-cell pertussis vaccine led to the production of an effective, less reactogenic pertussis vaccine culminating in the development of purified component (acellular) pertussis vaccines (41). Incorporation of DTaP has become the preferred vaccine for childhood vaccination (28).

The only contraindication specific to the use of DTaP/DTP is encephalopathy within 7 days of administration of a previous dose. The contraindications general for all vaccines also apply (see previous discussion). Precautions for the use of DTaP/DTP include (a) fever of 40.5°C or higher within 48 hours after vaccination with prior dose and not attributable to another identifiable cause; (b) collapse or shocklike state within 48 hours of receiving prior dose; (c) convulsions within 3 days of receiving prior dose; (d) persistent inconsolable crying lasting 3 hours or more, within 48 hours of receiving prior dose; and (e) Guillain-Barré syndrome within 6 weeks of prior dose (32).

Dosage

DTaP and DTP are combinations used in infants and children younger than 7 years. Universal use of DTaP or DTP in infancy and childhood is recommended unless contraindications exist (28). Tetanus and diphtheria toxoid (i.e., Td vaccine) absorbed (for adult use) is used in persons 7 years of age or older. Single-antigen tetanus toxoids are available for use in persons 7 years of age or older. Td vaccine is the recommended formulation for routine booster inoculation in older children, adolescents, and adults.

The usual dose for these vaccines is 0.5 mL intramuscular. The recommended schedule is to receive DPaT or DPT vaccine at 2 months, 4 months, 6 months, and 15 to 18 months of age. Td vaccine is recommended at age 10 to 11 years, followed by a booster every 10 years.

Use During Pregnancy or Lactation

No increased risk to mother or fetus from vaccination with Td or T vaccine during pregnancy, including in the first trimester, has been demonstrated (8,33,36). Widespread vaccination with tetanus toxoid of pregnant women in developing countries with high rates of neonatal tetanus has demonstrated the safety and the efficacy of this approach (32). In the United States, administration of Td vaccine is recommended for pregnant women who have not completed a primary series of vaccination or who are due for a booster (8,33).

Measles, Mumps, And Rubella

Background

Widespread vaccination of children against MMR has dramatically reduced the incidences of these infections and their associated complications worldwide (9,11,42,43 and 44). Measles is a ubiquitous, highly contagious infection that before vaccine availability, affected nearly 100% of the population by adolescence (42). In the United States during the pre–measles virus vaccine era, approximately 500,000 cases of measles were reported annually, with an estimated actual 4 million cases annually (45). The morbidity and mortality associated with measles was also extensive, with an estimated annual occurrence of 150,000 cases of respiratory complications (pneumonia); 100,000 cases of otitis media; 48,000 hospitalizations; 7,000 seizure episodes; 4,000 cases of encephalitis, of which 25% had permanent neurologic sequelae or deafness; and 500 deaths (45). After measles virus vaccine licensure in the United States, the incidence of measles was dramatically reduced, from a reported 450,000 cases in 1965 to 100 cases in 1998 (less than 1 case per 1 million population), of which 71% were associated with international importation, suggesting measles is no longer an indigenous disease in the United States (39). On a global basis, dramatic control of measles has been accomplished in many areas (42). However, measles still remains the leading cause of vaccine-preventable deaths in children (42). In the Global Burden of Disease Study, measles ranked eighth overall as a cause of mortality, with 1 million deaths worldwide in 1996 (46).

Before the licensing of live attenuated mumps virus vaccine in 1967, mumps was a common communicable disease of childhood. As noted by Plotkin and Wharton (43), the morbidity of mumps is best appreciated when the disease is perceived as a respiratory infection that is often accompanied by viremia resulting in multiorgan involvement, predominantly salivary glands. Complications of mumps are more common in adults and include orchitis in postpubertal men, pancreatitis, central nervous system involvement (meningoencephalitis), mastitis, nephritis, arthropathy, and myocarditis (rare) (43). In addition, mumps is a major cause of sensorineural deafness. Postlicensure of mumps virus vaccine, the reported cases of mumps in the United States declined from 152,209 in 1968 to 666 cases in 1998 (39,43). Similar dramatic decreases have accompanied the introduction of mumps virus vaccine globally.

Rubella was also a common infection of children and young adults before vaccine availability. In the United States, rubella was both endemic and epidemic, with a cycle of major epidemics at 7-year intervals (44). Rubella was generally perceived to be a benign disease until Gregg (47), an Australian ophthalmologist, suggested that rubella infection of pregnant women was associated with congenital cataracts. Subsequently, his findings were expanded to include congenital heart disease and deafness as the classic triad of the congenital rubella syndrome (44). The last major epidemic of rubella in the United States occurred from 1964 to 1965 and clearly demonstrated the significant adverse effects of rubella in pregnancy and congenital rubella (48). During the epidemic, an estimated 12.5 million cases of rubella occurred, with approximately 2,000 encephalitis cases reported. In pregnant women, there were 5,000 elective abortions, 6,250 spontaneous abortions, and 2,100 neonatal deaths or infants who were stillborn. Congenital rubella syndrome was noted in 20,000 surviving infants, of whom 11,600 were deaf, 3,580 blind, and

approximately 1,800 were mentally retarded. In addition, arthralgias and arthritis are common complications of rubella in adults; thrombocytopenia and encephalitis are less common (44). A syndrome of progressive rubella panencephalitis rarely occurs (49) and Guillain-Barré syndrome after rubella has been reported (50).

Since licensing of rubella vaccine in 1969 in the United States, no major epidemics of rubella have occurred and the incidence of disease (rubella and congenital rubella syndrome) has progressively declined (39,51). In 1998, only 364 cases of rubella were reported to the CDC and 7 cases of congenital syphilis (39). Of these cases, 71% were in persons 20 years of age or older, many of whom were immigrants who had not received vaccinations.

Indication

MMR vaccines are all live attenuated vaccines. These three vaccines are combined into a combination vaccine, which has been licensed in the United States since 1971. (42,43 and 44). In the United States, the ACIP has recommended two doses of MMR for all children and certain high-risk adolescents and adults (Fig. 25.1) (29). All children should receive the first dose of MMR vaccine at 12 to 15 months of age. The second dose should be administered at age 4 to 6 years; if the dose at age 4 to 6 years is missed, it is recommended that MMR vaccine be given at age 11 to 12 years. Although the second dose is primarily given to provide adequate protection against measles, it is recommended that both doses be given as MMR by both the Committees on Infectious Diseases of the AAP and the ACIP (42,43 and 44).

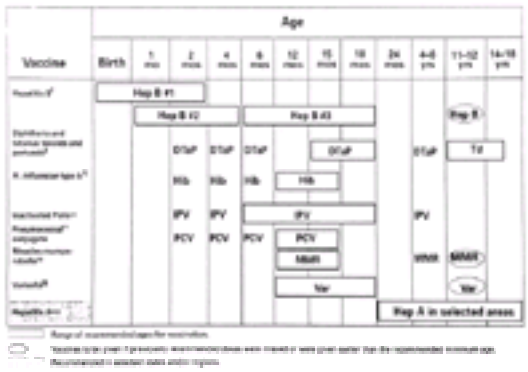


FIGURE 25.1. Recommended childhood immunization schedule—United States, January to December 2001. DTaP, diphtheria toxoid, tetanus toxoid, and acellular pertussis; DTP, diphtheria toxoid, tetanus toxoid, and pertussis; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; Td, tetanus and diphtheria toxoids; MMR, measles, mumps, and rubella; Var, varicella.

In addition to the recommended routine schedule of immunization with MMR vaccine, vaccination is recommended for all susceptible persons unless there is a contraindication. Persons born before 1957 are likely to have been naturally infected with MMR and thus can be considered immune (9). However, in the case of rubella, it is critical to ensure that women of childbearing age even those born before 1957,

are immune to rubella. Thus, adult women before pregnancy and adult seronegative pregnant women in the postpartum period have been targeted for rubella vaccine. In the United States, persons are considered susceptible to MMR unless they (a) have documentation of adequate vaccination (two doses after age 12 months); (b) have laboratory proof of immunity; or (c) have evidence of physician-diagnosed measles or rubella (9). Among adults, particular groups have been the focus for vaccination of susceptible individuals. These include (a) attendees of college or other higher educational institutions; (b) health care workers; (c) military recruits; and (d) international travelers (9). Susceptible adults should receive two doses of MMR separated by at least 28 days. In addition, anyone inoculated between 1963 and 1967 with killed vaccine (measles) or a vaccine of unknown type should be reinoculated (9).

Specific Contraindications/Complications

In general, MMR vaccine is contraindicated in (a) pregnant women (theoretical risk with live attenuated virus); (b) patients with moderate to severe illness or a high fever; (c) persons with a history of anaphylactic reaction to neomycin (measles virus vaccine), gelatin (mumps virus vaccine), or egg (mumps virus vaccine); (d) administration of Ig within 3 months; or (e) immunosuppression (42,43 and 44). History of allergy to eggs (without) anaphylaxis is generally not believed to be a contraindication to MMR vaccination (42,43 and 44).

Side effects associated with measles virus vaccines are generally mild and limited to susceptible vaccinees (Table 25.4) (5,8,9,21,42,52). Fever 39.4°C (103°F) or higher occurs in approximately 5% to 15% of vaccine recipients; it is usually not bothersome but rarely may induce febrile seizures (42). Rash occurs in about 5% of recipients (42). These side effects are less frequent with the second dose of vaccine because most individuals are already immune. The IOM found evidence to establish a casual relationship between measles virus vaccine and anaphylaxis, thrombocytopenia, and death from vaccine strain viral infection in severely immunocompromised persons (21). A relationship between measles virus vaccine and central nervous system effects such as encephalitis or encephalopathy has been debated; the IOM report concluded that inadequate data were available to accept or reject such a casual relationship (21).

The most common side effects associated with mumps virus vaccine are parotitis and low-grade fever (43). Rash, pruritus, and purpura, although reported, are uncommon, mild, and transient (43). The rate of aseptic meningitis after vaccination with the Jeryl Lynn strain used in the United States is very low at 1 of 800,000 (53). Moreover, sequelae to postvaccinal meningitis have been rare or absent (43).

Adverse events after rubella vaccination have also been a topic of controversy (44). Low-grade fever and rash occur in 5% to 10% of rubella virus vaccine recipients (9). Approximately 25% of susceptible adult women have transient arthralgias after rubella vaccination, and acute arthritis occurs in approximately 10% of susceptible women (54,55). The IOM review concluded that the rubella virus vaccine is an established cause of acute arthritis (21). However, the finding that the data also favored a casual role for the rubella virus vaccine in chronic arthritis (21) has been refuted by more recent studies (25,26). Furthermore, the IOM found insufficient data demonstrating a causal relationship between rubella and radiculoneuritis, other neuropathies, and thrombocytopenia (21). In contradistinction, Plotkin (44) concluded

that thrombocytopenia is causally associated with RA27/3 vaccination.

Dosage

Use of the combined MMR vaccine is encouraged for most indications. However, monovalent forms of the MMR vaccine are also available for use in specific circumstances (e.g., rubella virus vaccine postpartum for susceptible pregnant women). In the United States, and increasingly so in other areas of the world, most childhood vaccination is accomplished with a triple vaccine containing the Moraten attenuated measles virus (1,000 $TCID_{50}$), the Jeryl Lynn strain of mumps virus (5,000 $TCID_{50}$), and the RA27/3 rubella virus (1,000 $TICD_{50}$). $TCID_{50}$ is the median "tissue culture infective dose" of a virus. Measles virus vaccine is also combined only with the rubella vaccine as an alternative approach in adults.

Either as the combined MMR or as monovalent vaccines, the dosage is 0.5 mL given subcutaneously. Two doses are recommended for routine childhood immunization, as discussed previously. For adults, two does are required for measles, but single doses are sufficient for rubella and mumps when used in the monovalent form. Either as combined MMR or as monovalent vaccines in the recommended schedule, MMR vaccines are very effective and probably provide lifelong immunity (42,43 and 44).

Use During Pregnancy or Lactation

On theoretical grounds, MMR vaccines (combined or monovalent) should not be administered to pregnant women (9,42,43 and 44). The rationale for such a recommendation is that these are live attenuated vaccines that may produce a viremia with the potential for transplacental passage to the fetal compartment. Thus, it is recommended that women of childbearing age should avoid pregnancy for 3 months after vaccination with these live attenuated vaccines.

Measles virus vaccine has not been demonstrated to cross the placenta and infect the fetus (42). There is no evidence that measles or mumps virus vaccine can cause congenital malformations in humans (9,42,43). Although transplacental passage of virus has rarely been documented, evidence of fetal damage from the rubella virus vaccine does not exist (56,57,58,59 and 60). Specifically, there have been no documented cases of congenital rubella syndrome in the offspring of 226 susceptible women who received the RA27/3 rubella virus vaccine (strain currently used) within 3 months of conception and who carried their pregnancies to term (60). As a result, the ACIP recommends that rubella vaccination during pregnancy should not by itself be a reason to undertake an elective abortion (35). However, although no observable risk is associated with the rubella virus vaccine given during pregnancy, the rubella virus vaccine should not knowingly be given to a pregnant women (9).

The MMR vaccine or monovalent forms of the MMW vaccine are safe for use in breast-feeding women (9). Although live viruses may replicate and be excreted in the breast milk, the neonate is usually not infected and any infection is well tolerated (32,36). The widespread use of the rubella virus vaccine in seronegative pregnant women clearly demonstrates the safety of the use of these vaccines in breast-feeding women.

Hepatitis B Vaccine

Background

Hepatitis B virus (HBV) is transmitted by percutaneous or permucosal contact with HBV-containing body fluids, sexually by exposure to an infected partner, or perinatally from an infected mother to her infant (61). Based on seroprevalence data from the National Health and Nutrition Examination Survey, an estimated 5% of persons (12.5 million persons) living in the United States have been infected with HBV—approximately 300,000 persons each year during the 20 years preceding the survey (62).

In the United States, it is estimated that there are more than 1 million chronic carriers of HBV (i.e., individuals with chronic HBV infection) and that currently post–hepatitis B vaccine availability, 100,000 to 150,000 people are still infected each year (61,62,63 and 64). Furthermore, it is estimated that 5,000 people die each year in the United States as the result of HBV-related liver disease. Groups at high risk for HBV infection in the United States include (a) injection drug abusers; (b) men having sex with men; (c) persons having heterosexual contact with multiple partners; (d) household contacts of person with chronic HBV infection; (e) hemophiliacs; (f) hemodialysis patients and staff; (g) inmates of long-term correctional facilities; (h) persons with occupational exposure to blood and infected body fluids; (i) institutionalized persons with developmental disabilities; and (j) immigrants from geographic areas where HBV infection is endemic (63,64).

The public health impact of HBV infection is even more dramatic worldwide (61). An estimated 5% of the world's population (300 million people) have chronic HBV infection, which is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (65). Beasley (66) demonstrated that persons with chronic HBV infection have more than a 100-fold increased risk to develop hepatocellular carcinoma. It is estimated that 500,000 to 1,000,000 people die each year worldwide as the result of HBV-related liver disease (61,65).

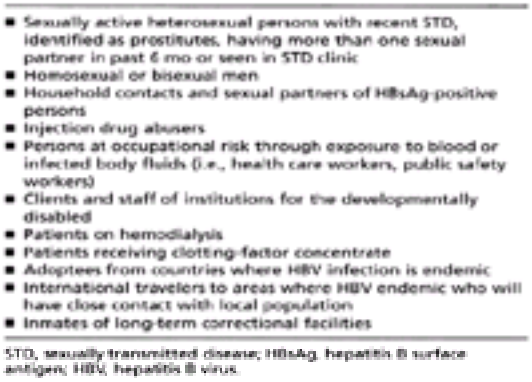
Both in the United States and in other areas of the world, the availability of the hepatitis B vaccine has led to significant declines in the incidence of HBV disease (39,61,67,68). In Taiwan, the incidence of liver cancer in children was reduced after the introduction of newborn universal vaccination (68).

Indications

The ACIP has developed recommendations for the prevention of HBV transmission in the United States (64). These recommendations address both preexposure vaccination and postexposure vaccination.

Preexposure vaccination to prevent HBV infection addresses three groups: (a) routine vaccination of infants; (b) catch-up vaccination of children and adolescents; and (c) vaccination of adults in high-risk groups (61,64). The hepatitis B vaccine is recommended for all infants; infants born to mothers who are hepatitis B surface antigen (HBsAg) positive should receive the first dose of vaccine within 12 hours of birth concomitantly with HBIG, whereas those born to HBsAg-negative mothers

should receive the first dose within 2 months of birth. All children and adolescents not previously inoculated with hepatitis B vaccine should be inoculated with the age-appropriate dose of vaccine; it is recommended that all 11 to 12 year olds be offered hepatitis B vaccine to ensure comprehensive coverage of all adolescents not inoculated at birth. Lastly, postexposure vaccination is recommended for adults in high-risk groups, as listed in Table 25.6, who have not previously been inoculated.



- Sexually active heterosexual persons with recent STD, identified as prostitutes, having more than one sexual partner in past 6 mo or seen in STD clinic
- Homosexual or bisexual men
- Household contacts and sexual partners of HBsAg-positive persons
- Injection drug abusers
- Persons at occupational risk through exposure to blood or infected body fluids (i.e., health care workers, public safety workers)
- Clients and staff of institutions for the developmentally disabled
- Patients on hemodialysis
- Patients receiving clotting-factor concentrate
- Adoptees from countries where HBV infection is endemic
- International travelers to areas where HBV endemic who will have close contact with local population
- Inmates of long-term correctional facilities

STD, sexually transmitted disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

TABLE 25.6. GROUPS AT HIGH RISK FOR HEPATITIS B INFECTION

Postexposure prophylaxis with hepatitis B vaccine to prevent HBV infection is recommended for (a) the prevention of perinatal HBV infection; (b) persons with accidental percutaneous or permucosal exposure to blood; (c) sexual partners of people with acute HBV infection; and (d) household contacts of persons with acute HBV infection. All pregnant women should be screened for HBsAg early in prenatal care. HBsAg-negative women at high risk of HBV infection (Table 25.6) should be retested during the early third trimester. Infants born to HBsAg-positive women should receive the first vaccine dose plus HBIG within 12 hours of birth. Women admitted for delivery who were not screened prenatally should have blood drawn for HBsAg screening, but the infant should receive the hepatitis B vaccine within 12 hours of birth while the result is pending.

Specific Contraindications/Complications

The initial hepatitis B vaccines consisted of purified inactivated HBsAg particles obtained from the plasma of chronic HBV carriers. In the United States, the plasma-derived vaccines have been replaced by recombinant DNA vaccines derived from yeast.

Adverse effects after hepatitis B vaccine are uncommon and consist mainly of local reactions or low-grade fever. Anaphylaxis occurs rarely, but other serious adverse events have not been shown to be caused by the hepatitis B vaccine. The only specific contraindication to the hepatitis B vaccine is a history of allergy to yeast.

Dosage

The hepatitis B vaccine should be administered according to the recommended doses and schedule listed in Table 25.7. Administration of the vaccine should be in the deltoid muscle of children, adolescents, and adults or in the anterolateral thigh of neonates and infants (61). Comvax combines PedvaxHIB (*H. influenzae* type b conjugate) and Recombivax HB vaccines for administration at 2 months, 4 months, and 12 to 15 months of age in infants of HBsAg-negative mothers.

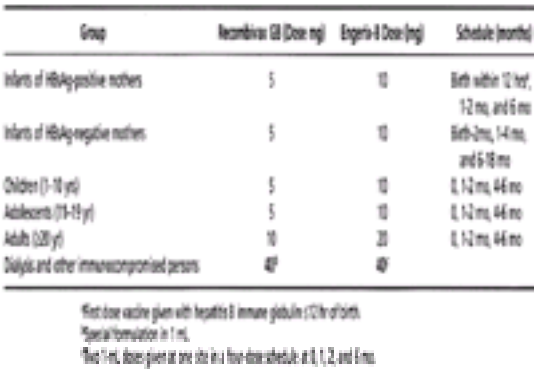


TABLE 25.7. RECOMMENDED DOSES AND SCHEDULES OF HEPATITIS B VACCINE

After three doses of hepatitis B vaccine, 95% to 99% of persons have protective antibody titers. There is a steady decline in protective antibody titers over time (61). However, studies have failed to identify acute cases of HBV among vaccine responders. Asymptomatic infections have been detected in 2.6% of persons followed for up to 11 years, but none had evidence of chronic HBV infection (61). These asymptomatic infections do not produce the sequelae associated with chronic HBV infection (61). To date, it has been demonstrated that the hepatitis B vaccine provides protection against serious HBV infection for at least 12 years (61). At this time, in the United States, routine booster doses of the hepatitis B vaccine are not recommended for persons who responded to vaccination (61).

Use During Pregnancy or Lactation

The hepatitis B vaccine is safe to use in pregnant and breast-feeding mothers. Recombinant vaccines contain noninfectious DNA particles, so there is no risk to the fetus or breast-feeding infant. Thus, neither pregnancy nor lactation is a contraindication to the hepatitis B vaccine.

Hepatitis A Vaccine

Background

Hepatitis A virus (HAV) infection is usually a mild self-limited disease without any

chronic sequelae (69). In 1998, there were 23,229 cases of HAV reported in the United States (39). The CDC estimates that there were 90,000 cases of symptomatic HAV infection and overall 180,000 persons had HAV infection (39). The mortality rate with HAV infection is low, with an estimated 100 persons dying each year in the United States as the result of acute liver failure due to fulminant HAV (69). No chronic carrier state exists for HAV infection.

In developing countries of the world where HAV infection is endemic, HAV infection is nearly universal in childhood (69). However, HAV disease in childhood is usually subclinical (69). In the United States, risk factors associated with HAV infection have been identified (70). These include (a) personal contact with infected person; (b) staff and children in day care centers; (c) international travel to geographic areas in which hepatitis A is endemic; (d) homosexual men; (e) injection drug abusers; and (f) staff and patients of institutions for developmentally challenged persons. Approximately 45% of persons with sporadic community-acquired hepatitis do not have an identified risk factor (70).

Indication

The hepatitis A vaccine is recommended for persons 2 years of age or older who are at increased risk of HAV infection (9,69). Preexposure vaccination is indicated for (a) international travelers to countries where hepatitis A is endemic; (b) military personnel; (c) high-risk ethnic or geographic populations (e.g., Native Americans and Alaskan natives); (d) homosexual or bisexual men; (e) intravenous drug abusers; (f) regular recipients of blood or plasma-derived products (e.g., factor VIII); (g) persons engaged in high-risk employment (e.g., primate handlers, employees of institutions for developmentally challenged, and staff of day care centers); and (h) persons chronically infected with hepatitis C (40% chance of developing fulminant disease if infected with HAV) (71).

Vaccination should also be considered for food handlers and children 2 years of age or older in group day care centers (69). The ACIP recommends that children living in states, counties, or communities where the reported annual rates of hepatitis A were more than or equal to 20 per 100,000 between 1987 and 1997 should be routinely inoculated with the hepatitis A vaccine at 2 years of age or older (72). In addition, the hepatitis A vaccine should be considered for all children living in states, counties, or communities with reported annual rates of HAV between 10 to 20 per 100,000.

Contraindications/Complications

Two inactivated hepatitis A vaccines are available in the United States, Havrix (SmithKline Beecham Biologicals) and Vaqta (Merck and Company). No serious side effects have been associated with either of these vaccines (9). Local reactions at the injection site are common but mild (9).

The only contraindication for hepatitis A vaccine is a history of allergy to any vaccine components (73). In children younger than 2 years, currently available hepatitis A vaccines are not approved for use.

Dosage

Havrix is available in two concentrations (69). The 720 enzyme-linked immunosorbent assay units (EU) per milliliter formulation is designed as a pediatric vaccine in persons aged 2 through 18 years and is administered in three 0.5 mL (360 EU) intramuscular injections at 0, 1, and 6 to 12 months. The formulation with 1,440 EU/mL can be used for either pediatrics or adults; the pediatric dose is 0.5 mL (720 EU) and the adult dose at 1 mL (1,440 EU) administered as an intramuscular injection, followed by a booster 6 to 12 months after the primary dose for individuals with repeated or long-term exposure.

Vaqta is available as 50 U/mL. For children and adolescents (2 to 18 years of age), a single dose of 0.5 mL (25 units) is recommended. A single 1-mL dose (50 units) is recommended for adults. At 6 to 12 months, a booster dose is recommended to provide long-term protection (9,69).

These inactivated hepatitis A vaccines are highly immunogenic and provide protection against infection for at least 10 years in persons receiving the primary vaccine and the booster (69).

In Europe a third hepatitis A vaccine, Avaxim, is licensed for use in persons older than 15 years (69). It is administered intramuscularly as a 0.5-mL injection, followed by a booster dose 6 to 12 months later.

Use During Pregnancy Or Lactation

Hepatitis A vaccines are inactivated viruses. Thus, hepatitis A vaccine is not specifically contraindicated in pregnancy. However, it should be given only if clearly needed (e.g., with exposure to infected contact or travel to endemic area). Similarly, hepatitis A vaccine is safe in breast-feeding mothers.

Varicella Vaccine

Background

Varicella-zoster (VZ) virus is a very contagious virus that is spread by respiratory droplets or airborne transmission (74,75). Acute varicella (chickenpox) most commonly occurs in childhood, but susceptible adults may also acquire VZ (74,75). Chickenpox is one of the most communicable human infections (75). As a result, more than 90% of persons in temperate climates have been infected by the age of 20 (74). As noted by Gershon (75), until vaccination against varicella becomes universally used, chickenpox will continue to be endemic in the United States.

An estimated 4 million cases of varicella occur annually in the United States (74,75). In addition, it has been estimated that 5.2 million cases of herpes zoster (recurrent form of VZ virus infection) occur each year in the United States (76). Worldwide, an estimated 60 million cases of varicella occur annually (77). Balducci et al. (78) calculated the incidence of varicella in pregnancy to be 7 cases per 10,000 pregnancies. Thus, an estimated 2,800 pregnant women each year develop acute varicella.

Healthy children produce few extracutaneous manifestations of varicella (74,75). These are uncommon and include pneumonitis, encephalitis, cerebellar ataxia, arthritis, hepatitis, glomerulonephritis, pericarditis, and orchitis (74,75). In contradistinction, adults with varicella have more morbidity associated with primary VZ virus infection (74,79,80). In adults, fever is higher and of longer duration and the severity of constitutional symptoms such as malaise, myalgias, and dehydration is greater (74). Complications of varicella such an encephalitis, pneumonia, and hepatitis are more common and more severe in adults. For instance, encephalitis occurs seven times more often in adults than in healthy children (74). Adults with varicella complications are hospitalized nine times more often than children and have a case fatality rate that is estimated to be 25 times more than that associated with children (81,82). The CDC estimates that 60 to 100 previously healthy persons die of varicella complications annually in the United States (83).

The morbidity of acute varicella is increased in varicella-susceptible pregnant women and their fetuses (75). Gershon (75) reviewed reported cases of varicella in pregnancy and noted that among the 198 cases, 57 (29%) women developed pneumonia and the case fatality rate for pneumonia was 28% (16 of 57). As for the fetus, Patuszak et al. (84) in their metaanalysis estimated that the risk of congenital varicella syndrome is 2% if acute varicella occurred during the first 20 weeks of gestation (84).

Indications

The Oka varicella vaccine was licensed in Japan in the late 1980s and in the United States in 1995 (74). The ACIP recommended universal use of varicella vaccine for all healthy, varicella-susceptible children 12 months to 12 years of age (83). As the primary target, it is recommended that all children should be routinely inoculated at 12 to 18 months of age (83,85). To maximize vaccine compliance, the ACIP recommends review of vaccination status at 11 to 12 years of age and administration of varicella vaccine to those not previously inoculated or infected with chickenpox (83).

Persons 13 years of age or older should be assessed for varicella immune status, and those who are susceptible should be inoculated (83). Those with a reliable history of varicella are considered immune (83). In the absence of such a history, patients are considered susceptible and can be either tested to determine their immune status or inoculated without testing (83). The ACIP recommends that priority should be given to vaccination of susceptible adolescents and adults who are at high risk for exposure and for transmitting varicella (83). Vaccination is recommended for susceptible persons who have close contact with persons at high risk for serious complications (e.g., health care workers, family contacts of immunocompromised persons). Vaccination should be considered for susceptible persons in the following groups who are at high risk for exposure: (a) persons living or working in environments in which transmission of VZ virus is likely (e.g., teachers of young children, day care employees, and residents and staff in institutional settings); (b) persons living or working in environments in which varicella transmission can occur (e.g., college students, inmates and staff of correctional institutions, and miliary personnel); (c) nonpregnant women of childbearing age; and (d) international travelers. Women in the reproductive age-group should be asked if they are pregnant and advised to avoid pregnancy for 1 month after vaccination (83). Vaccination of

other susceptible adolescents and adults is desirable and may be offered during routine health care visits (83).

Specific Contraindications and Complications

Varicella vaccine, which is a live attenuated vaccine, is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine, including neomycin or gelatin (83). Varicella vaccine is not recommended for persons with active, untreated tuberculosis. It is contraindicated for use in persons with malignant conditions affecting the bone marrow or lymphatic system (83). However, varicella vaccine is available on a compassionate basis for use in patients with acute lymphoblastic leukemia who (a) have disease that has been in remission for 12 continuous months; (b) have a negative history of varicella; (c) have a peripheral lymphocyte count of more than 700 cells/mm^2; and (d) have a platelet count of more than 100,000 cells/mm^2 within 24 hours of vaccination (83).

Varicella vaccine should not be administered to persons with primary or acquired immunodeficiency, including HIV infection or AIDS, cellular immunodeficiencies, hypogammaglobulinemia and dysgammaglobulinemia; varicella vaccine is also contraindicated in patients on immunosuppressive therapy (e.g., high-dose steroids and cancer chemotherapy) (83). Varicella vaccine in pregnancy is contraindicated (see later discussion) (83).

The most common side effects seen with varicella vaccine are mild tenderness and redness at the infection site (15% to 20%), fever (10% to 15%), and mild rash (1% to 5%) (74,83). Transmission of vaccine virus to healthy susceptible persons has occurred rarely, but the disease is invariably mild or subclinical (74). This risk is higher if a rash develops and may be higher with immunocompromised vaccines (74,83).

Dosage

Varicella vaccine is a live attenuated VZ virus known as the Oka strain (83). The vaccine contains more than 1,350 plaque-forming units in each 0.5-mL dose. Children 12 years of age or younger should be administered one 0.5-mL dose of vaccine subcutaneously (83). Preferably, varicella virus vaccine should be administered routinely to children at the same time as MMR vaccine (12 to 18 months of age) (83). Persons 13 years of age or older should receive two 0.5-mL doses of vaccine subcutaneously 4 to 8 weeks apart (83).

The seroconversion rate after one dose of vaccine among susceptible children 12 months to 12 years of age is 97% (83). Among adolescents and adults 13 years of age or older, 78% of vaccines seroconverted after the first dose, and 99% seroconverted after a second dose (83). In clinical trials, varicella vaccine has proven to be effective for more than 10 years in preventing varicella (9,83). Most vaccinees who acquire varicella tend to have mild illness. Overall, varicella vaccine provides 70% to 90% protection against acute varicella infection and 95% protection against serious disease for more than 10 years (9,86).

Use During Pregnancy and Lactation

Varicella vaccine is a live attenuated virus and thus because of a theoretical risk of viremia and transplacental passage of vaccine virus to the fetus, pregnant women should not be inoculated with varicella vaccine (74,83). In addition, it is recommended that vaccine recipients should not become pregnant within 1 (ACIP) or 3 (Merck) months of vaccination (74,83). However, no infants with the congenital varicella syndrome secondary to vaccine-type virus have been reported (74,87). The manufacturer (Merck) in collaboration with the CDC has established the Varivax Pregnancy Registry to monitor maternal-fetal outcomes of pregnant women inadvertently administered varicella virus vaccine 3 months before or during pregnancy (telephone, 800-986-8999) (87). Initial results demonstrated no evidence of congenital varicella syndrome among 257 livebirths followed prospectively (95% confidence interval, 0–0.1%). Moreover, the risk of congenital varicella syndrome with wild virus is low (83), with an estimated 0.4% with maternal infection from conception to 12 weeks and 2% when infected between 13 to 20 weeks (78,84,88). The virulence of the attenuated vaccine virus is less than that of the wild type virus, so the risk to the fetus, if any, should be even lower (83). Thus, although a pregnant woman who inadvertently was inoculated within 1 month of conception or during pregnancy should be counseled about potential effects on the fetus, a decision to terminate a pregnancy should not be based on whether vaccine was administered just before or during pregnancy (83).

According to the CDC, varicella virus vaccine may be administered to nursing mothers (83). It is not known whether attenuated vaccine virus is excreted in human milk and whether infants can be infected (83). However, most live vaccines (rubella is exception) have not been demonstrated to be secreted in breast milk (83).

Pneumococcal Vaccine

Pneumococcal infections caused by *Streptococcus pneumoniae* remain an important cause of morbidity and mortality (89,90). Major clinical syndromes associated with *S. pneumoniae* include otitis media, sinusitis, bronchitis, and pneumonia, which occur secondary to direct spread of the organism from the nasopharynx (89,90). Hematogenous spread of *S. pneumoniae* can result in meningitis, endocarditis, arthritis, or peritonitis (89,90). Population-based studies have demonstrated that the overall rate of invasive pneumococcal disease (i.e., isolation of *S. pneumoniae* from a normally sterile site such as blood, pleural fluid or cerebrospinal fluid) is about 15 per 100,000 persons per year (89). Certain populations such as Native Americans have an incidence rate up to tenfold higher (90). Invasive pneumococcal infection is common in newborns and infants 2 years of age or younger and among adults 65 years of age or more (90). Among persons 65 years of age or older, the incidence of mortality was 42 to 57 cases per 100,000 population (89). Approximately 200,000 cases of invasive pneumococcal disease occur annually in the United States, with nearly 40,000 deaths per year (91).

In the United States, pneumococcal infection is the leading cause of community-acquired pneumonia requiring hospitalization, with 30% to 50% of such cases caused by *S. pneumoniae* (89,90). The mortality rate for community-acquired pneumonia is 5% to 10% overall, increasing to 10% to 30% in people 65 years of age or older (91). Most fatal cases of pneumococcal pneumonia are associated with bacteremia (89). Conversely, 70% to 90% of pneumococcal bacteremia is caused by pneumococcal pneumonia (89). The mortality rate associated with pneumococcal

bacteremia range from 16% to 36% among adults and 28% to 51% among persons 65 years of age or older (89,90).

Risk factors that predispose to pneumococcal infection have been identified (90). These include (a) defective antibody formation (congenital or acquired); (b) patients with multiple myeloma, lymphoma, or chronic lymphocytic leukemia; (c) HIV infection; (d) neutropenia from any cause; (e) persons 65 years of age or older; (f) chronic diseases; and (g) prior respiratory viral infection, particularly caused by influenza virus (90).

Over the past two decades, *S. pneumoniae* has increasingly become more resistant to penicillin and other antibiotics (92,93 and 94). This clearly has major implications for the treatment and complications of pneumococcal disease.

Indications

Recommendations for the use of pneumococcal vaccine have been promulgated by the ACIP, most recently in 1997 (95). The ACIP strongly recommends vaccination with pneumococcal vaccine for all persons 65 years of age or older and for those persons between 2 and 65 years of age who are at increased risk for serious pneumococcal infection. Those at increased risk include (a) persons with functional or anatomic asplenia (e.g., sickle cell disease, splenectomy); (b) persons with chronic cardiovascular or pulmonary disease; (c) those with diabetes mellitus; (d) alcoholics and those with chronic liver disease; (e) persons with cerebrospinal fluid leak; and (f) persons inhabiting special environments (e.g., nursing homes, chronic care facilities, homeless shelters) or social settings (e.g., Native Alaskan, Native American) (95). Disappointingly, large national surveys have demonstrated that only 30% to 35.6% of persons 65 years of age or older in the United States have received pneumococcal vaccine (96,97).

Although pneumococcal vaccine is less effective in immunocompromised persons, it is still recommended (95). The rationale is both the increased risk of pneumococcal disease in these groups and benefits, safety, and low cost of vaccination with pneumococcal vaccine. Thus, patients in the following groups should be inoculated with pneumococcal vaccine: (a) HIV infection; (b) congenital immunodeficiency; (c) leukemia, lymphoma, Hodgkin disease, and multiple myeloma; (d) generalized malignancy; (e) chronic renal failure; (f) nephrotic syndrome; and (g) organ or hematopoietic cell transplantation (95).

Routine revaccination with pneumococcal vaccine is not recommended in the United States (95). Revaccination once is recommended for persons 65 years of age or older who received vaccine more than 5 years before the age of 65. Revaccination once after 5 years is also recommended for persons with asplenia or who are immunocompromised (95).

Specific Contraindications and Complications

Other than a severe reaction to a previous dose of vaccine, there are no contraindications to pneumococcal vaccine. Local side effects are common, with 30% to 50% of recipients of pneumococcal vaccine experiencing erythema, induration, and pain (90,95,98). These reactions are generally mild and of short

duration (1 to 3 days). Severe systemic reactions are uncommon and severe febrile reactions (more than 103°F) are extremely rare (89).

Dosage

Pneumococcal vaccine is a polysaccharide vaccine that contains the capsular polysaccharides of 23 serotypes of *S. pneumoniae.* These serotypes are responsible for approximately 90% of invasive pneumococcal disease in developed countries (89). In the United States, two pneumococcal vaccines are marketed: Pneumovax 23 (Merck and Company) and Pnu-Imune 23 (Lederle Laboratories).

Pneumococcal vaccine is administered as a single 0.5-mL dose intramuscularly or subcutaneously. The intramuscular route is preferred (95). The duration of immunity is unclear and revaccination should be considered after 5 years in patients at high risk of decline in antibody levels (e.g., those with chronic renal failure, nephrotic syndrome, or organ transplants) or of fatal infection (asplenia) (95).

Although not as effective as most monovalent vaccines (90% to 95% or more), the efficacy of pneumococcal vaccine is still good (89). Overall effectiveness rate approaches 60%, and in patients 65 years of age or older, the effectiveness rate is 75% (89). To overcome the limitations of the 23-valent pneumococcal polysaccharide vaccine, newer pneumococcal conjugate and protein vaccines have been developed (89). Initial results with pneumococcal conjugate vaccines have been very encouraging (99,100 and 101). However, conjugate vaccines are only effective against the serotypes included in the vaccines. Thus, research currently is attempting to identify other protective antigens—primarily proteins essential to pneumococcal virulence for candidate pneumococcal protein vaccines (89).

Use During Pregnancy Or Lactation

The safety of pneumococcal vaccine for use in pregnant women has not been determined (89). However, there is no reason to suspect that vaccination with pneumococcal vaccine, even in the first trimester, would have an adverse effect on the fetus or mother (89). Thus, pneumococcal vaccine use is not contraindicated in pregnancy. However, its use should be limited to those pregnant women at high risk (see “Indications”) not previously inoculated. Ideally, such high-risk women should be inoculated before rather than during pregnancy (89).

Pneumococcal vaccine is safe to use in breast-feeding women. In fact, it has been suggested that maternal vaccination may stimulate protection in newborns via breast milk (89).

Influenza Vaccine

Background

Influenza is an acute febrile, prostrating infection of sudden onset that primarily involves the respiratory tract (e.g., nonproductive cough, nasal discharge, and substernal burning) but is associated with systemic symptoms of myalgia and headache that are out of proportion to the severity of respiratory symptoms (102). In

adults, gastrointestinal symptoms are uncommon. Primary influenza virus pneumonia is rare except in persons with chronic cardiopulmonary disease; if it occurs, it is usually fatal (102). Secondary bacterial pneumonia is responsible for most fatal cases of influenza (102).

Human influenza viruses are classified into three types: A, B, and C (102). Influenza A infection is the most frequent, is associated with the most morbidity and mortality, and is responsible for worldwide pandemics (104). Influenza B causes regional epidemics that are less severe than influenza A epidemics, but influenza B does not cause pandemics (104). Influenza C rarely causes epidemics (104). Because influenza A and B cause epidemic human disease, influenza vaccines contain two strains of A and one strain of B (102,103). Influenza A is divided into two subtypes based on surface antigens, hemagglutinin and neuraminidase (103). Influenza B is not categorized into subtypes. Both influenza A and B are further separated into groups based on antigenic characteristics (103). Frequent antigenic charges (antigenic drift) due to point mutations that occur during viral replication result in new influenza variants (103). This antigenic drift is the virologic basis for seasonal epidemics and why each year's influenza vaccine contains one or more new strains of influenza virus (103). Major antigenic differences (antigenic shift) occur at irregular intervals of 10 to 40 years (102). As a result of antigenic shift, viruses with major antigenic differences from prevalent subtypes circulate in the community. Because these subtypes are antigenically unique, they are rapidly dispersed, resulting in widespread (pandemic) disease, affecting all age-groups (102). In the past century, such pandemics occurred in 1918, 1957, and 1968 (102).

Influenza epidemics occur nearly every year during the winter months and the CDC estimates that influenza is responsible for approximately 20,000 deaths per year in the United States (103). Rates of infection are highest in children, but rates of serious illness and mortality are highest in person 65 years of age or older or in persons of any age with existing medical conditions associated with a high risk for complications (103). During the pandemic of 1957 to 1958 and the subsequent epidemic during 1960, pregnant women, particularly during the third trimester, were also noted to be at higher risk for influenza-associated disease (105,106 and 107).

The devastating impact of influenza was best demonstrated during the pandemic of 1918 to 1919, when there were 20 million deaths worldwide and 500,000 deaths in the United States (102). The risks for complications, hospitalization, and deaths from influenza are highest in persons 65 years of age or older, very young children, and persons of any age with certain underlying medical conditions (103). During the past two decades, the estimated number of influenza-associated hospitalizations in the United States ranged from approximately 20,000 to more than 300,000 per epidemic, with an average of approximately 114,000 excess hospitalizations per year related to influenza (103). It has been estimated that the annual economic cost of influenza in the United States is $3 to $5 billion annually (108).

According to the CDC, vaccination levels in persons 65 years of age or older increased from 33% in 1989 to 63% in 1997 (103). This rate exceeded the Healthy People 2000 goal of 60% (109). However, the vaccination for persons younger than 65 years with high-risk conditions was less than 30%, well short of the Healthy People 2000 goal of 60%. Moreover, only 34% of health care workers reported that they received influenza vaccine (110). Thus, there clearly exists the need to increase influenza vaccination utilization, which will in turn lead to a significant improvement in

public health (102).

As reviewed by the CDC, influenza vaccine is effective in preventing secondary complications and reducing the risk for influenza-related hospitalizations and deaths among persons 65 years of age or older and those with chronic diseases that place them at high risk for such complications (103,111). Among the older adult population not residing in nursing homes or chronic care facilities, influenza vaccine is 30% to 70% effective in preventing hospitalizations for influenza and pneumonia (103,112,113). Although vaccination prevents only 30% to 40% of influenza infection in elderly persons residing in nursing homes, influenza vaccine is effective in this group at preventing severe illness, secondary complications, and deaths; vaccine prevents 50% to 60% of hospitalizations or pneumonia and 80% of the mortality (103). Nichol et al. (114) demonstrated that influenza vaccination in healthy young adults significantly reduced the frequency of upper respiratory tract infection by 25%, work absenteeism by 36% to 43%, and physician office visits for upper respiratory tract infection by 44% (114).

Indications

The ACIP strongly recommends that influenza vaccine be given to any persons 6 months of age or older who because of age or underlying medical condition are at increased risk for complications of influenza (103). In addition, it is recommended that health care workers and other individuals (including household members) in close contact with persons in high-risk groups be inoculated (103).

Vaccination with influenza vaccine is recommended for the following groups of persons who are at increased risk for complications from influenza, who have a higher risk for complications from influenza, or who have a higher prevalence of chronic medical conditions that place them at risk for influenza-related complications: (a) persons aged 50 years or older; (b) residents of nursing homes and other chronic care facilities that house persons of any age who have chronic medical conditions; (c) adults and children who have chronic pulmonary or cardiovascular disease, including asthma; (d) adults and children with chronic metabolic diseases (e.g., diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; (e) children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and might be at risk for developing Reye syndrome after influenza infection; and (f) women who will be in the second or third trimester of pregnancy during the influenza season (103). In addition, the ACIP recommends that the following persons who can transmit influenza be inoculated: (a) physicians, nurses, and other personnel in both hospital and adjacent outpatient care settings; (b) employees of nursing homes and chronic care facilities who have contact with patients or residents; (c) persons who provide home care to persons in high-risk groups, and (d) household members (including children of persons in high-risk groups) (103).

Additional groups in which influenza vaccine is recommended include (a) pregnant women who will be beyond the first trimester of pregnancy during the influenza season; (b) HIV-infected patients; and (c) any persons who wish to reduce the likelihood of acquiring influenza (103).

Specific Contraindications and Complications

Inactivated influenza vaccine should not be administered to persons with a history of anaphylactic hypersensitivity to eggs or other components of influenza vaccine (102,103). Some authorities believe that most persons with a history of egg allergy can be inoculated, although it should be approached with caution (102). The CDC suggests that persons who have developed hives, have had swelling of lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to determine whether vaccine should be administered (103). Protocols have been developed for safely administering influenza vaccine to persons with egg allergies (115,116).

Influenza vaccines are contraindicated in infants younger than 6 months and only split-virus vaccines should be used in children from 6 months to 12 years of age (102). In addition, adults with acute febrile illnesses should not be inoculated until their symptoms have abated. However, minor illnesses with or without fever are not contraindications for use of influenza vaccine (103).

The CDC suggests that when educating patients about potential side effects, it should be emphasized that (a) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza and (b) coincidental respiratory disease unrelated to influenza vaccination can occur postvaccination (103). Local reactions (e.g., erythema, pain, tenderness, and itching) are the most frequent side effects of influenza vaccination, effecting 10% to 64% of patients and lasting up to 2 days (102,103). These local reactions are generally mild and rarely interfere with daily activities (103). Systemic reactions include fever, malaise, myalgias, headache, and arthralgia. These are uncommon (e.g., 1% of adults develop moderate fever) and most often affect individuals who have had no exposure to the influenza virus antigens in the vaccine (e.g., young children) (103). These systemic reactions begin 6 to 12 hours postvaccination and may persist for 24 to 48 hours (103). The high incidence of febrile reactions to whole-virus vaccine in infants and children (8% to 50%) has led to the use of a two-dose immunization schedule and administration of split-virus vaccine to children younger than 12 years (102).

Immediate allergic reactions including hives, angioedema, allergic asthma, and systemic anaphylaxis rarely occur after influenza vaccination (115). Most reactions are probably induced by residual egg protein in the vaccine (see previous discussion for details) (103).

Several neurologic syndromes have been temporally associated with influenza vaccination (102). These include rare instances of optic neuritis, brachial neuritis, and cranial palsies; however, no statistically significant association with influenza vaccine has been established (102). However, a statistically significant association for Guillain-Barré syndrome with influenza vaccine was established *only* with the swine influenza vaccine of 1976 (102,103). The CDC emphasizes that no large increases in Guillain-Barré syndrome associated with influenza vaccine (other than swine influenza vaccine in 1976) have been noted, and that if influenza vaccine does pose a risk, it is probably quite small, slightly more than one case per million people inoculated (103). During epidemics from 1972 to 1973 through 1994 to 1995, the estimated rates of influenza-associated deaths ranged from approximately 300 to more than 1,500 per million persons no younger than 65 years of age (90% of

influenza mortality occurs in this group) (103). Thus, the potential benefit of influenza vaccine in preventing serious illness, hospitalization, and death greatly outweighs the possible risk (if any) for developing influenza vaccine-associated Guillain-Barré syndrome.

Dosage

Influenza vaccine is an inactive virus vaccine composed of three influenza virus strains; usually two strains of influenza A and one strain of influenza B (102,103). The WHO makes recommendations as to the antigenic properties of influenza virus strains for use in influenza vaccines each year (102). It is recommended that influenza vaccine should be administered before influenza outbreaks occur, which is from December through March (103). The optimal time for vaccination against influenza is from the beginning of October through mid-November (103).

Dosage recommendations for influenza vaccine vary according to age-group (103). Among adults, a single 0.5-mL intramuscular injection is recommended (103). Adults should be inoculated in the deltoid muscle. Children younger than 9 years should receive two doses administered at least 1 month apart. Children younger than 12 years should be inoculated with split-virus vaccine, whereas adults generally receive whole-virus vaccine (103).

In the United States, three influenza virus vaccines are licensed and available (102). These are Fluzone (Connaught), Fluvirin (Evans), and Flu-Shield (Wyeth-Ayerst).

Use During Pregnancy and Lactation

Currently available influenza vaccines are inactivated viral vaccines and thus are considered safe to use during any stage of pregnancy (103). Heinoven et al. (117) demonstrated no adverse fetal effects associated with influenza vaccine in a study of more than 2,000 pregnant women inoculated with influenza vaccine (117). Several other studies also evaluated antepartum influenza vaccination and documented no adverse effects on mother or infant (118,119 and 120). Some experts prefer to wait until after the first trimester of pregnancy is completed to administer influenza vaccine (as well as all vaccines) (103).

Excess deaths due to influenza were documented among pregnant women during the pandemics of 1918 to 1919 and 1957 to 1958 (106,121,122 and 123). Additional studies have suggested that pregnancy can increase the risk for serious medical complications of influenza as a result of the many physiologic changes associated with pregnancy, including increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function (e.g., decreased cell-mediated immunity) (107,124,125). euzil et al. (126) reviewed the impact of influenza during 17 interpandemic influenza seasons and demonstrated that the relative risk for hospitalization for selected cardiorespiratory conditions among pregnant women increased from 1.4 during weeks 14 to 20 of gestation to 4.7 during weeks 37 to 42, compared with women who were 1 to 6 months postpartum. In this study, women in the third trimester were hospitalized at a rate of 250 per 100,000 pregnant women, a rate comparable to that of nonpregnant women who had high-risk medical conditions for serious influenza infection (103). Based on the data in the study by Neuzil et al. (126), an average of one to two hospitalizations could be

prevented for every 1,000 pregnant women inoculated (103,126).

Thus, the benefit of influenza vaccination during pregnancy outweighs the potential risks. Women who will be beyond the first trimester of pregnancy (no less than 14 weeks of gestation) during the influenza season should be inoculated (103). Some experts suggest that all women at any stage of pregnancy should be inoculated against influenza before the influenza season. Pregnant women who have medical conditions that increase their risk for complications from influenza should be inoculated before the influenza season, regardless of the stage of pregnancy (103).

Influenza vaccine does not affect the safety of mothers who are breast-feeding or their infants (103). Furthermore breast-feeding does not adversely affect the mother's immune response (103). Thus, breast-feeding is not a contraindication for vaccination with influenza vaccine.

Lyme Disease Vaccine

Lyme disease is a multisystem illness that primarily affects the skin, joints, heart, and nervous system (127,128). It is a tick-borne disease caused by infection with the spirochete *Borrelia burgdorferi* (128). Lyme disease is a multistage disease (127,128). Early localized disease manifests with skin lesions, erythema migrans, and within days or weeks, some infected patients undergo lymphatic or hematogenous dissemination of the organism to multiple organs, resulting in multiple skin lesions, hepatitis, cranial and peripheral neuropathies, meningitis, encephalitis, heart block and myocarditis, and arthritis (127). In the untreated or inadequately treated patient, *B. burgdorferi* infection can progress to late disseminated disease (127,128). The most common manifestation of late Lyme disease is intermittent swelling and pain of one or more joints, usually large weight-bearing joints such as the knee (128). Some cases manifest with chronic axonal polyneuropathy or encephalopathy, which presents with cognitive disorders, sleep disturbance, fatigue, and personality changes (128). Since the CDC initiated surveillance for Lyme disease in 1982, the number of annually reported cases in the United States has increased approximately 25-fold (128). In 1998, there were 16,801 cases of Lyme disease reported, the highest number ever reported (39). In the United States, the disease is primarily localized to states in the northeastern, mid-Atlantic, and upper north central regions and to several areas in northwestern California (129). The following nine states had incidence rates higher than the annual national average of 6.39 cases per 100,000 population and accounted for 93% of reported cases: Connecticut (105 of 100,000), Rhode Island (79.6), New York (25.5), New Jersey (24.0), Pennsylvania (22.9), Maryland (13.1), Massachusetts (11.5), Wisconsin (12.8), and Delaware (10.7) (39).

Two Lyme disease vaccines, which use recombinant *B. burgdorferi* lipidated outer surface protein A (OspA) as immunogen, have been developed (128): LYMErix (SmithKline Beecham Biologicals) and ImuLyme (Pasteur Merieux Connaught). Only LYMErix is licensed by the Food and Drug Administration and available for use in the United States.

Indications

Recently the CDC issued recommendations for use of Lyme disease vaccine (128).

Lyme disease vaccine is recommended for persons who reside, work, or recreate in areas of high or moderate risk for acquiring Lyme disease; Lyme disease vaccination should be considered for individuals aged 15 to 70 years who engage in activities that result in frequent or prolonged exposure to tick-infected habitat. Lyme disease vaccination may be considered for persons age 15 to 70 years with exposure to tick-infected habitats that is neither frequent nor prolonged. Vaccination should be considered for travelers to areas of high incidence if frequent or prolonged exposure to tick-infected habitats is anticipated. Vaccination should also be considered for persons with a history of previous uncomplicated Lyme disease who are at continued high risk.

Specific Contraindications and Complications

Until the safety and immunogenicity of recombinant OspA vaccines in children have been established, Lyme disease vaccine is not recommended for children younger than 15 years (128). Similarly, the safety and efficacy of Lyme disease vaccine have not been established for persons older than 70 years (128). Because the safety of recombinant OspA vaccines administered during pregnancy has not been established, vaccination of pregnant women is not recommended (128). Because persons with HIV, joint swelling, or diffuse musculoskeletal pain were excluded from the phase III Safety and Efficacy Trial of Lyme Disease Vaccine, no data exist regarding vaccine use in these groups (128).

In the phase III clinical trails of LYMErix, nearly 5,000 vaccine and 5,000 placebo recipients were compared (130). Soreness at the injection site was the most frequent side effect, occurring in 24.1% of vaccine recipients, versus 7.6% of placebo recipients. Redness and swelling at the injection site occurred in less than 2%; myalgia, influenza-like illness, fever, and chills were noted in up to 3.2%. Arthralgias were more common in vaccine recipients. No episodes of immediate hypersensitivity reactions among vaccine recipients were noted.

Dosage

LYMErix is administered by intramuscular injection, 0.5 mL (30 µg), into the deltoid muscle (128). Three doses are required for optimal protection (128,130). The first dose is followed by a second dose 1 month later and a third dose administered 12 months after the first dose. Vaccine administration should be timed so that the second dose (year 1) and the third dose (year 2) are given several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April (128).

Use During Pregnancy and Lactation

The safety of recombinant OspA vaccines administered during pregnancy has not been studied. Thus, vaccination of women known to be pregnant is not recommended (128).

No evidence has demonstrated that pregnancy increases the risk to acquire Lyme disease or its severity (128). Moreover, acute Lyme disease during pregnancy responds well to antibiotic therapy and adverse fetal or maternal outcomes have not

been reported in pregnant women receiving standard courses of treatment (128).

SmithKline Beecham Biologicals (manufacturer of LYMErix) has established a Lyme disease vaccine pregnancy registry for pregnant women inadvertently inoculated. Health care providers are encouraged to register such vaccination by calling the company (800-366-8900, ext. 5231).

Immune Therapy

Passive immunization to provide temporary protection against specific infections is accomplished by injection of Ig containing exogenously produced antibody (9). This can be pooled human Ig or hyperimmunoglobulin obtained from persons with known high titers of antibody to a specific infectious agent.

Immune Globulin

Ig is a preparation made up of pooled human Igs containing antibodies against infectious agents, particularly hepatitis A and measles (9). Ig is indicated for postexposure or preexposure prophylaxis depending on the infectious agent of concern.

In the case of exposure to hepatitis A, Ig is effective in preventing disease when administered within 14 days of exposure. The postexposure dose of immunoglobulin G (IgG) to prevent HAV is 0.02 mL/kg intramuscularly (9,131). Ig is an alternative to hepatitis A vaccine as prophylaxis for short-term exposure (e.g., single international trip of less than 2 to 3 months' duration). For preexposure prophylaxis (i.e., international travel), the dose is 0.06 mL/kg intramuscularly (9,131). The efficacy of Ig for the prevention of HAV is 80% to 90% if given early in the incubation period.

The other major indication for Ig is postexposure prophylaxis for measles (9,131). Ig may prevent or modify measles if administered within 6 days of exposure (9). The dose of Ig to prevent measles is 0.25 mL/kg intramuscularly for healthy persons; maximum total dose is 15 mL (9,131).

Other than a history of anaphylactic reaction to Ig, there is no contraindication to the use of Ig. The most common side effect is local tenderness; rarely anaphylaxis has occurred (9). Ig inhibits the immune response to live virus vaccines (e.g., measles and rubella), for 3 months with hepatitis prevention dose and 5 months with measles prevention dose (9,132). Ig is safe for use in pregnant and lactating women.

Hepatitis B Immune Globulin

HBIG is hyperimmunoglobulin prepared from plasma that has been preselected to contain high titers of antibody against HBsAg (9). HBIG is recommended for postexposure prophylaxis in susceptible persons who have been exposed to blood or body fluids containing HBsAg by percutaneous or mucous membrane routes or by HBV-infected sexual partners (9,64,131). HBIG is also recommended for infants born to HBsAg-positive women (64).

In adults, for both sexual contacts and percutaneous exposure, the dose is 0.6 mL/kg

intramuscularly given immediately. For newborn passive immunization, a dose of 0.5 mL should be given within 12 hours of delivery (64). The hepatitis B vaccine series should be started in conjunction with HBIG in adults and newborns (64). For percutaneous and sexual exposures, postexposure prophylaxis with HBIG is 75% effective. Used in combination with hepatitis B vaccine, HBIG is more than 90% effective in neonates (61,64,68).

There are no known contraindications or precautions with HBIG (9). The use of HBIG in pregnant and breast-feeding women appears to be safe.

Varicella-Zoster Immune Globulin

VZIG is a hyperimmunoglobulin prepared by obtaining serum from individuals with high titers of VZ antibodies. VZIG is recommended for postexposure prophylaxis against varicella in susceptible immunocompromised persons with significant exposure to varicella such as household contact, close contact indoors of more than 1 hour, sharing same hospital room, or prolonged direct face-to-face contact (83). In addition, VZIG is recommended for susceptible pregnant women exposed to varicella and newborns delivered to mothers who developed clinical varicella within 5 days before to 48 hours after delivery (83).

In adults, the dose of VZIG is 125 units per 10 kg of body weight (maximum of 625 units) intramuscularly. VZIG should be administered within 96 hours of exposure (83). It has been suggested that VZIG may also be useful in ameliorating the clinical presentation of varicella in susceptible adults, particularly pregnant women who may be at increased risk for complications of varicella (9,83).

Local reactions (e.g., pain, redness, and swelling) are uncommon (less than 10%) and severe side effects are rare (83). There are no known contraindications to VZIG (9,83).

VZIG is safe to use in pregnant and breast-feeding women (83). Its primary benefit is to decrease the incidence and severity of maternal varicella (83). However, its effect on vertical transmission of varicella is unknown.

Use Of Vaccines: Special Circumstances

Table 25.2 and Table 25.5 summarize those immunizations that are routinely recommended in adults. However, there are special circumstances in which various additional vaccines are recommended (Table 25.8).

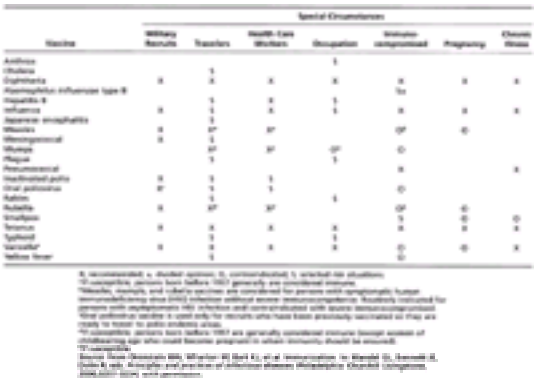


TABLE 25.8. SPECIAL CIRCUMSTANCES FOR IMMUNIZATIONS IN ADULTS

Pregnancy

Immunization of pregnant women is generally not recommended because of theoretical risks to the fetus (3,9,27,32). However, in certain circumstances, selected vaccines may be indicated when the benefits of vaccinating a pregnant woman outweigh any potential risks (3,9,27,32,33,133). Such instances include (a) if the risk of infection is high; (b) if the infection can have serious consequences for the pregnant woman or her fetus; and (c) if the vaccine is unlikely to be associated with an increased incidence of adverse effects (33,133). A summary of vaccines that are recommended for use in pregnant women either on a routine basis or in selected high-risk situations is provided in Table 25.9.

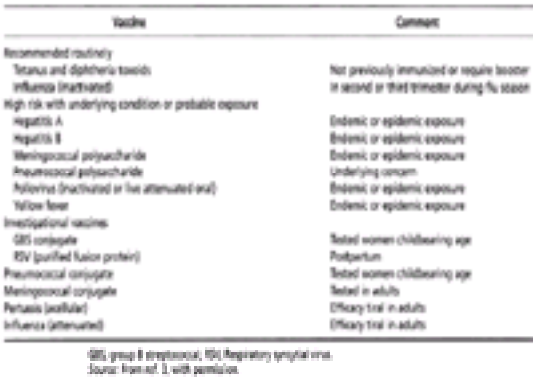


TABLE 25.9. SUMMARY OF VACCINES FOR PREGNANT WOMEN

In general, live organism vaccines are contraindicated in pregnancy because they contain attenuated viruses or bacteria that multiply in the vaccine recipient (3,9,32). In particular, the live virus vaccines, some of which prevent infections such as rubella and varicella that are known to be teratogenic, are usually contraindicated in

pregnancy (32,33,36,133). However, it is recommended that both OPV vaccine and yellow fever vaccine can be administered to nonimmune pregnant women who are at substantial risk of imminent exposure to infection (e.g., international travelers to endemic areas) (23,33,134). Unfortunately, despite warnings, some pregnant women are inadvertently inoculated with live virus vaccines. Studies, to date, have demonstrated the safety of such inadvertent vaccination in pregnancy (35,83). Moreover, the risk to the fetus is largely theoretical (9,32). Thus, administration of a live virus vaccine during pregnancy, including rubella or varicella, is not an indication for performing an abortion to terminate the pregnancy (35,83). As discussed in earlier sections, the Rubella Vaccination in Pregnancy Registry documented the apparent safety of inadvertent rubella vaccination in pregnancy (35) and currently there exists a Varicella Vaccination in Pregnancy Registry to monitor prospectively maternal and fetal outcomes in pregnant women inadvertently injected with varicella vaccine (telephone, 800-986-8999) (36,83,87).

Killed and inactivated vaccines do not contain viruses or bacteria that can multiply within the body and thus do not pose a risk during pregnancy. In the past, concern arose over the use of inactivated poliovirus (IPV) vaccine and suspected association of IVP vaccine use in pregnancy with neural malignant neoplasms in offspring (117). However, other studies have not confirmed this association and IPV vaccine can be provided to pregnant women requiring immediate protection against poliomyelitis (23,33,36).

No adverse effects on pregnant women or their fetuses have been demonstrated with the use of other killed inactivated vaccines and toxoids (9,32,33,36). In fact, these vaccines and toxoids are indicated in pregnancy to prevent infections associated with serious adverse events in the mother or fetus. Thus, influenza vaccine is recommended on a routine basis for pregnant women who will be in the second or third trimester during the influenza season because influenza has been associated with increased morbidity in pregnant women (103). An example of protection for the fetus or neonate is vaccination of pregnant women with tetanus toxoid in developing areas of the world where neonatal tetanus is a common and devastating disease (32). Maternal immunization provides protection to the newborn as the result of transplacental passage of maternal IgG antibodies to the fetus. In the United States, administration of combined tetanus-diphtheria toxoid is recommended for any pregnant women who have not completed their primary vaccination series or who need a booster dose (33,133). Hepatitis B vaccine is produced with recombinant DNA technology and contains no infectious agent. Thus, it also is safe to use when indicated in pregnant women at high risk for acquiring HBV (64).

Because of theoretical concerns, some physicians prefer to avoid vaccination during the first trimester of pregnancy and wait until after 14 weeks of gestation to administer vaccines or toxoids to pregnant women (133). In reality, there is no evidence demonstrating that there is an increased risk to the mother or fetus with vaccination in the first trimester (32). Furthermore, in some cases, vaccination will be required before 14 weeks of gestation (32). Thus, vaccines such as influenza vaccine, hepatitis B vaccine, and tetanus-diphtheria toxoid may be given in the first trimester (33,64,103,133).

Neither live nor killed vaccines are contraindicated in breast-feeding mothers (30,33). No adverse events in mother or infant have been associated with vaccination of breast-feeding mothers (30,33). The killed or inactivated virus vaccines do not

multiply within the body and thus carry no risk for lactating mothers or their infants (30). Although live virus vaccines contain attenuated live viruses or bacteria that replicate in vaccine recipients, most live viral or bacterial vaccines have not been demonstrated to be secreted in breast milk and thus are not a risk to lactating women or their infants (32). Thus, it is recommended that lactating mothers may also receive live virus vaccines such as MMR, varicella, rubella, OPV, and yellow fever safely (33,35,83,133). Attenuated rubella virus vaccine is an exception and has been detected in breast milk and from the nasopharynx and throat of some breast-fed infants (135). However, no adverse effects have been noted and rubella vaccination postpartum is commonly performed.

International Travel

Various vaccines are required for admission into some countries or are recommended for travelers to countries where vaccine-preventable diseases are endemic (136). Information can be obtained by calling the CDC Travel Information System at 404-332-4559. Examples of vaccines commonly considered for travelers include measles, polio, and tetanus-diphtheria boosters. Travelers to endemic areas should consider hepatitis B, hepatitis A, typhoid, yellow fever, rabies, plague, and Japanese encephalitis prophylaxis (32).

Occupational Exposure

Vaccine recommendations have not been promulgated for most occupational categories (32). However, specific recommendations have been established for health care workers (137). All health care workers and public safety workers who may be exposed to blood or blood-derived body fluids should receive hepatitis B vaccine. Any health care worker who may transmit rubella to pregnant patients should be immune to rubella vaccine. In addition, health care workers are at greater risk of measles than the general population and should receive measles virus vaccine (two doses) if they are susceptible. To prevent transmission of influenza to patients at high risk for complications of influenza, all health care workers should receive influenza vaccine before the influenza season annually (103). Varicella vaccination is also recommended for health care workers not immune to varicella (83).

There are other occupations at need for selected vaccination. These include plague vaccine for laboratory workers with potential exposure to plague and anthrax vaccine for animal workers.

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