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109 Infections of the Female Pelvis

Richard H. Beigi

SHORT VIEW SUMMARY

Definition
- An acute inflammation of the epithelium and/or soft tissue of the pelvic organs

Microbiology
- Microorganisms found in the endocervix and vagina
- Bacterial vaginosis microorganisms, predominantly anaerobes
- Group B *Streptococcus* and *Escherichia coli*
- Sexually transmitted microorganisms, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

Diagnosis
- Clinical diagnosis based on fever, erythema, and tenderness in the postoperative setting
- Clinical diagnosis based on risk assessment for sexually transmitted disease and an evaluation for lower genital tract inflammation in the case of pelvic inflammatory disease

Therapy for Postoperative Infections
- Broad-spectrum antibiotic therapy
- Include coverage of penicillinase-producing anaerobes
- Use antibiotic regimens effective in an anaerobic environment

Therapy for Pelvic Inflammatory Disease
- Be aware of the emerging resistance of *N. gonorrhoeae* to quinolones, azithromycin, and, to some degree, cephalosporins
- Treat concurrently for bacterial vaginosis if the diagnosis is made concurrently

Prevention
- Preoperative antibiotic prophylaxis
- Screening for sexually transmitted microorganisms

Infections of the female pelvis can be conveniently considered in three basic categories: infections related to pregnancy, infections occurring after gynecologic surgery, and pelvic inflammatory disease (PID), with its associated conditions and implications. Pelvic infections are commonly polymicrobial, with cultures revealing a mixture of both aerobic and anaerobic bacteria. These pathogenic microorganisms frequently originate from the flora of the lower genital tract. The microbial etiology of even hospital-acquired intrapartum, postpartum, and postsurgical infections reflects this because isolation of bacteria resistant to broad-spectrum antibiotic therapy is uncommon.

INTRAPARTUM, POSTPARTUM, AND POSTABORTAL INFECTIONS

Intraamniotic infection (IAI), commonly referred to as chorioamnionitis, is a clinically detectable infection of the amniotic fluid and fetal membranes during pregnancy.[1] IAI occurs in up to 10.5% of women in labor.[2] Most cases of IAI originate when vaginal microorganisms ascend into the intrauterine cavity after rupture of the membranes.[3] Approximately 2% of women with preterm labor (<37 weeks of gestation) and intact membranes have symptomatic chorioamnionitis, whereas another 20% have subclinical infection. Of women receiving ampicillin and erythromycin therapy for preterm-premature rupture of the membranes, approximately 15% will develop IAI compared with a 26% incidence for those not treated with antibiotics.[4] In full-term pregnancies, IAI is associated with dysfunctional labor. Approximately 75% of infected women require augmentation of labor with oxytocin, and approximately 35% require cesarean delivery, usually because of arrest of progress in labor.[5] A few cases, most notably those caused by *Listeria monocytogenes,* result from transplacental hematogenous spread in mothers with bacteremia.[6] The diagnosis is usually made before membrane rupture in these patients. Rare cases of IAI occurring after diagnostic amniocentesis, intrauterine transfusion, or percutaneous umbilical blood sampling have been reported. Intrauterine infection can also occur after cervical cerclage (a circumferential suture about the cervix to prevent preterm delivery in women with cervical insufficiency) in 1% to 2% of patients, and this risk may be as high as 25% if the cerclage is performed after prolapse of the membranes into the vagina. Risk factors for IAI include prolonged duration of labor or rupture of membranes, multiple vaginal examinations, young age, low socioeconomic class, nulliparity, and preexisting bacterial vaginosis.[5]

Microorganisms, such as lactobacilli and diphtheroids, are commonly found in the amniotic fluid of women in normal labor at term. Those with IAI have a select group of high-virulence microorganisms, such as group B streptococci, *Escherichia coli,* genital mycoplasmas, and pathogenic anaerobes (e.g., *Prevotella bivia*), present in significantly higher quantities, causing an inflammatory response and systemic signs of infection.[3] The first two microorganisms are found most commonly when maternal and/or neonatal bacteremia complicates intraamniotic infection.[3] Many of these microorganisms, especially anaerobic bacteria, the mycoplasmas, and *Gardnerella vaginalis*, have also been associated with bacterial vaginosis.

The clinical diagnosis of IAI is imprecise and has recently been slightly changed.[7] It is based on the presence of an isolated fever of greater than or equal to 39.0°C (102.2°F) or a lower-grade temperature (>38°C [100.4°F]) that is present on two occasions 30 minutes or more apart and the presence of one other clinical finding: maternal leukocytosis (defined as a white blood cell [WBC] count >15,000/μL), purulent cervical drainage, or fetal tachycardia. The vast majority of these gravidas will have concomitant ruptured membranes. Practically, clinicians tend to base the diagnosis on the presence of intrapartum fever plus one additional criterion anyway.[8] Maternal and/or fetal tachycardia are common with fever and add little additional information. Although the abdomen should be examined for uterine tenderness, it is often obscured by conduction anesthesia. Foul-smelling amniotic fluid is rarely appreciated. Maternal WBC counts increase with duration of labor, and cut-points suffer from a lack of precision to reliably distinguish fever from infectious and noninfectious causes. Furthermore, patients with preterm-premature rupture of the membranes before 32 weeks of gestation are candidates for antenatal steroid therapy to promote fetal lung maturity. Betamethasone leads to an increase in maternal leukocyte count and a decrease in lymphocyte count. These changes return to baseline within 3 days. Although the diagnosis is based largely on clinical findings, amniotic fluid Gram staining, WBC count (>50 cells/mm^3), and glucose concentration (<15 mg/dL) have been shown to be useful

in supporting the clinical impression, particularly in patients with intact membranes.[9] Microbial invasion of the amniotic cavity is accompanied by the presence of high amniotic fluid concentrations of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor, and a gelatinase, matrix metalloproteinase 9.[10] Measurement of these substances is costly and not readily available.

Given the imprecision of the diagnosis of IAI, antibiotic therapy should be considered in laboring gravidas with isolated fever (>39°C [102.2°F] once or >38.0°C [100.4°F] on two successive readings). Antimicrobial therapy for IAI is aimed at preventing bacteremia in the mother, as well as initiating intrapartum treatment of the fetus while awaiting delivery. Gibbs and colleagues[11] documented improved neonatal and maternal outcome when antibiotic therapy is begun intrapartum rather than immediately postpartum. Delivery of the fetus and placenta removes the sites of infection, much like draining an abscess, making this intervention the most significant part of therapy. Because group B streptococci and *E. coli* are the most common isolates from infected neonates, a combination of ampicillin plus gentamicin is a reasonable initial regimen for IAI. This regimen is sufficient to treat the mother if the delivery was vaginal, with only one additional dose of the antibiotic regimen needing to be administered postpartum. If cesarean delivery is required, up to 15% of operative patients given only ampicillin and gentamicin experience treatment failure by developing postpartum endometritis. These patients probably require continued broad-spectrum antibiotic coverage, including anaerobic coverage, and accordingly, a drug such as clindamycin and metronidazole should be added to the treatment regimen to decrease the risk for postpartum endometritis by half.[12] Other broad-spectrum regimens may be equally effective. This antibiotic regimen should be continued until the patient has been afebrile (temperature < 37.8°C [100°F]) for 24 hours.[13]

Although delivery is essential for cure, no critical diagnosis-to-delivery interval beyond which the frequency of neonatal complications escalates dramatically has been identified.[14] Accordingly, labor needs to be managed actively, but cesarean delivery should be performed only for accepted obstetric indications and not done solely for the presence of a clinical diagnosis of IAI.

Postpartum Endometritis

Postpartum infection of the uterus, the most common cause of puerperal fever, is designated endomyometritis. Cesarean delivery, particularly after labor or rupture of the membranes of any duration, is the dominant risk factor for postpartum endomyometritis (PPE).[15] The pathogenesis of this infection involves inoculation of the amniotic fluid after membrane rupture or during labor with vaginal microorganisms. The myometrium, leaves of the broad ligament, and the peritoneal cavity are then exposed to this contaminated fluid during surgery (Fig. 109.1). The reported incidence of PPE after cesarean delivery is less than 10% in patients receiving antibiotic prophylaxis. The diagnosis is uncommon after vaginal delivery. Risk factors for postcesarean endomyometritis include a prolonged duration of labor or rupture of the membranes, presence of bacterial vaginosis, number of vaginal examinations, and use of internal fetal monitoring.[16,17] Antimicrobial prophylaxis is associated with a 50% reduction in infection in all populations studied. All patients undergoing cesarean delivery, either elective or unscheduled, are candidates for antibiotic prophylaxis.[18] There is now strong evidence that antibiotic prophylaxis given for cesarean delivery before skin incision, rather than after cord clamping, decreases the incidence of postcesarean endomyometritis and total infectious morbidities without affecting neonatal outcomes.[19] In addition, a recently published randomized controlled investigation has demonstrated an additional 50% reduction in surgical site infections (SSIs) among women having a nonelective cesarean delivery during labor and/or after rupture of membranes with the addition of azithromycin to the antibiotic prophylaxis regimen.[20] Many patients who develop postcesarean endometritis despite antibiotic prophylaxis have histologic evidence of incipient infection.[21]

PPE is a polymicrobial infection caused by a wide variety of bacteria. Group B streptococci, enterococci, other aerobic streptococci, *G. vaginalis, E. coli, P. bivia, Bacteroides* spp., and peptostreptococci are the most common endometrial isolates, with group B streptococci and *G. vaginalis* the most common isolates from the blood.[22–24]

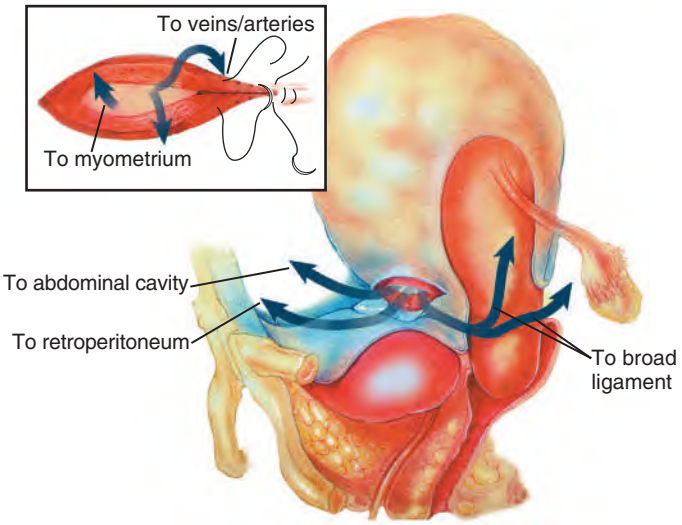

FIG. 109.1 Pathophysiology of postcesarean endomyometritis. Note the potential pathways for contaminated amniotic fluid to infect the postpartum pelvic tissues.

The isolation of *Ureaplasma urealyticum* and *Mycoplasma hominis* from endometrium and blood suggests that these organisms can cause PPE, although good clinical responses have been obtained in patients with mycoplasmas cultured from the blood and who were treated with antibiotics not active against these organisms. These organisms have also been reported to be important pathogens associated with abdominal wound infection after cesarean delivery.[25]

Chlamydia trachomatis has been associated with a late form of PPE that occurs more than 2 days to 6 weeks after delivery in women who deliver vaginally.[26] Group A β-hemolytic streptococcal endometritis is uncommon. The source of a sporadic postpartum group A β-hemolytic streptococcal infection is typically unknown, but outbreaks of postpartum and postsurgical group A β-hemolytic streptococcal infections have been associated with colonized health care workers. Health care workers who were asymptomatic carriers of group A β-hemolytic streptococci have been identified in 15 of 21 outbreaks of postpartum and postsurgical infections reported from 1976 to 2005.[27] The infections are characterized by early onset and rapid severe progression with few localizing symptoms or physical signs. These can sometimes also be fatal if unrecognized/untreated (and even occasionally with appropriate recognition and therapy).

The diagnosis of PPE is suggested by the development of fever, usually on the first or second postpartum day. Significant fever is defined as an oral temperature of 38.5°C (101.3°F) or higher in the first 24 hours after delivery or 38°C (100.4°F) or higher for at least four consecutive hours 24 or more hours after delivery. Other consistently associated findings are lower abdominal pain, uterine tenderness, and leukocytosis. These patients may also exhibit a delay of the normally rapid postoperative return of bowel function due to an associated local peritonitis.

Patients with suspected PPE should have the uterus assessed for size, consistency, and tenderness. This requires a bimanual pelvic examination in women in whom the uterus is no longer palpable on abdominal examination.

The value of transvaginally obtained uterine cultures and the optimal method of obtaining such cultures remain matters of controversy. Although cultures obtained transvaginally are often difficult to interpret because of contaminants, they may be useful for those patients in whom initial therapy fails.[28] A test for *Chlamydia* should be performed in patients with late-onset (>7 days after delivery) mild PPE, particularly those at high risk for chlamydial infection (e.g., adolescents).

Clindamycin plus gentamicin has proved to be the most effective regimen in treating PPE, especially if PPE occurs after cesarean delivery.[29] Alternative regimens used for the treatment of PPE include one of the extended-spectrum penicillins or second-generation cephalosporins (e.g., ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam,

cefotetan, cefoxitin). Failures of those regimens with poor activity against penicillin-resistant anaerobic bacteria (e.g., penicillin and gentamicin without clindamycin) are more likely. For this reason antimicrobial regimens used in the treatment of postcesarean endometritis should provide satisfactory coverage of penicillin-resistant anaerobic microorganisms (e.g., *P. bivia*). The carbapenems (imipenem-cilastatin, meropenem, ertapenem) have also proved effective in the treatment of these infections but are generally reserved for more resistant infections not usually found on an obstetric service.

Parenteral therapy should be continued until the patient's temperature has remained lower than 37.8°C (100°F) for 24 hours, the patient is pain free, and the leukocyte count is normalizing. The use of oral antibiotics after discharge has been shown to be unnecessary.[30] Women with late-onset PPE can be treated as outpatients with oral azithromycin or doxycycline therapy with or without metronidazole, depending on whether they have coexistent bacterial vaginosis. It is recommended if this is the chosen treatment route that timely clinical follow-up does occur to assure improvement and/or resolution. Doxycycline should be avoided in nursing mothers.

Early-onset PPE should respond to parenteral antimicrobial therapy within 48 hours, with the patient becoming afebrile within 96 hours. Failure to accomplish this goal frequently suggests the presence of an abdominal wound infection (or an alternative source), which occurs in 50% of these patients.[31] Because cephalosporin antibiotic prophylaxis is commonly administered to women undergoing cesarean delivery, enterococcal superinfection is another common explanation for failure to respond or relapse after treatment with regimens that are not effective against enterococci (e.g., extended-spectrum cephalosporins, clindamycin plus gentamicin). This is particularly true if the organism is isolated in pure culture or from heavy growth from an endometrial specimen. If an enterococcal superinfection is suspected, one of the following regimens should be used: (1) clindamycin or metronidazole plus ampicillin plus gentamicin, (2) ampicillin-sulbactam plus gentamicin; (3) cefoxitin or cefotetan plus ampicillin, (4) ticarcillin–clavulanic acid, or (5) piperacillin-tazobactam. Uncommonly, failure results from lack of coverage of a drug-resistant anaerobe; this can be corrected by a regimen containing either metronidazole or clindamycin. The importance of endometrial cultures for aerobes, anaerobes, and mycoplasmas will increase as antimicrobial resistance to clindamycin grows among isolates of gram-negative anaerobes.[32]

If fever persists despite apparently appropriate antimicrobial therapy, the differential diagnosis includes a wound or pelvic abscess, refractory postpartum fever, and noninfectious fever (e.g., drug fever, breast engorgement). Careful physical examination is the most important to distinguish between pelvic and nonpelvic causes of fever. Appropriate imaging studies, usually pelvic ultrasonography or computed tomography (CT), can confirm the presence of a pelvic hematoma or abscess, usually involving the space between the lower uterine segment and bladder. If present, percutaneous drainage by interventional radiology can be considered, and occasionally open surgery is required for complete management and resolution.

PPE caused by group A β-hemolytic streptococci has special epidemiologic significance.[33–35] The Centers for Disease Control and Prevention (CDC) recommends that health care worker screening be undertaken when two episodes of postpartum group A streptococcal infection are identified within a 6-month period. All health care workers present at the delivery and those who performed vaginal examinations before delivery should be screened with cultures of the nares, throat, vagina, rectum, and skin. Any health care worker who is culture positive for group A *Streptococcus* should refrain from patient care for the first 24 hours of antimicrobial therapy. If surveillance identifies additional patients or health care workers with positive cultures for group A *Streptococcus,* the isolates should be typed by sequencing the variable portion of the M-protein gene or other molecular methods to identify the strain.

Refractory Postpartum Fever of Undetermined Origin

Traditionally, the diagnosis of septic pelvic thrombophlebitis (SPT) was entertained in those patients with PPE refractory to broad-spectrum antimicrobial therapy. Once alternative explanations (e.g., wound infection, pelvic abscess, urinary tract infections, etc.) for persistent fever were ruled out, heparin therapy was used to determine whether the diagnosis was SPT or drug fever. Women with SPT responded promptly to therapeutic anticoagulation with heparin and became afebrile within 24 to 48 hours.[36] More recent analysis of this practice has made this therapeutic approach suspect.

Brown and colleagues[37] studied women who had pelvic infection and fever that persisted after 5 days despite adequate antimicrobial therapy with clindamycin, gentamicin, and ampicillin. A diagnosis of SPT was made after CT evaluation revealed uterine vein thrombosis. Women were randomly assigned to continuation of antimicrobial therapy, either alone or with the addition of heparin, until the temperature was lower than 37.5°C [99.5°F] for 48 hours. SPT (1:3000 deliveries) was diagnosed in 22% of women with prolonged infection. There was no significant difference between the responses of women with pelvic infection who were and were not given heparin therapy; in both groups, women required an average of 6 days of therapy before becoming afebrile. These results do not support the common empirical practice of heparin treatment for women with persistent postpartum infection.

Similarly, for an 8-year period (1986–94), Witlin and colleagues[38] reviewed the medical records of 31 postpartum women with the diagnosis of SPT. All of the patients demonstrated refractory febrile morbidity (mean, 5.5 ± 1.9 days before institution of heparin therapy) despite antimicrobial therapy with ampicillin, gentamicin, and clindamycin. Imaging studies (CT, ultrasonography, or both) revealed no pelvic pathologic process. The patients required an average of 4.7 ± 2.1 days (median, 5 days; range, 1–9 days) of heparin therapy before defervescence. Heparin levels were therapeutic at a mean of less than 24 hours (range, 6–24 hours). The authors suggested that currently available imaging studies cannot diagnose the entity we now define as SPT. In addition, their findings do not support the time-honored rule that SPT responds within 24 to 48 hours to therapeutic anticoagulation with heparin.

Taken together, these studies suggest that patients with refractory postpartum fever require more time to resolve their persistent fever than their more responsive counterparts and that anticoagulation does not speed this process along. Antibiotics should be discontinued in patients with persistent fever who look well, have a normal pelvic examination, and have no leukocytosis, considering the diagnosis of drug fever. More prolonged antibiotic therapy (5–6 days) with or without adjunct heparin therapy should be anticipated in those patients with persistent fever, continued pelvic organ tenderness, and persistent leukocytosis.[39]

Infections After Perineal Lacerations

Infection of the episiotomy site is an uncommon occurrence. Overall, only 0.1% of episiotomies become infected, although this rate increases to 1% to 2% for episiotomies complicated by third- or fourth-degree extensions. *Routine episiotomy is no longer recommended in obstetrics.* Modern obstetrics therefore deals with spontaneous perineal lacerations after vaginal delivery. A recent report suggests that women with third- and fourth-degree perineal tears have a lower rate of perineal wound complications if they receive antibiotic prophylaxis with cefoxitin or cefotetan at the time of repair.[40]

Shy and Eschenbach[41] classified episiotomy infections into four categories, depending on the depth of infection. The simple episiotomy infection is a local infection that is limited to the skin and superficial fascia along the episiotomy incision. In contrast to deeper infection, the associated skin changes of edema and erythema occur only adjacent to the episiotomy. The simple episiotomy infection may initially be treated with broad-spectrum antibiotics with activity against streptococci, staphylococci, Enterobacteriaceae, and anaerobes, including *Bacteroides fragilis.* If a therapeutic response is not prompt, the wound should be opened, explored, and débrided under adequate anesthesia to exclude hematoma or previously unrecognized rectovaginal communication. Ramin and colleagues[42] showed that with proper preoperative care, simple episiotomy infection is not a contraindication to early repair of dehiscence.

Infection of the two layers of the superficial fascia may occur. The more common is superficial fascia infection without necrosis, the clinical

presentation of which is neither striking nor distinctive. The skin may be erythematous and edematous, but severe systemic manifestations do not occur. If a response to broad-spectrum antibiotic therapy does not occur in 24 to 48 hours or if the clinical condition worsens during antibiotic therapy, then the episiotomy should be surgically explored.

Infection of the superficial fascia with necrosis, most commonly referred to as necrotizing fasciitis, is an uncommon yet severe infection of the subcutaneous tissues (i.e., the superficial fascia) that spreads in the fascial clefts overlying the deep fascia. The deep fascia usually, but not always, is spared; skin involvement results only secondarily, after the nutrient vessels to the skin thrombose. Because the skin is not primarily involved, the episiotomy wound may appear normal, making early recognition difficult and causing fatal delay in treatment. Despite the minimal local findings, patients may appear severely ill, with marked local pain, high fever, and prominent systemic manifestations. Most patients are diabetic. A definitive diagnosis is made at surgery, with the discovery of extensive undermining of surrounding tissues and lack of resistance in the superficial fascial plane to probing with a blunt instrument. Treatment includes broad-spectrum antibiotics (e.g., clindamycin plus ampicillin plus gentamicin) and radical débridement to include removal of all necrotic and pale tissue. It should be emphasized that treatment of this disease is primarily surgical and that less than aggressive resection of all involved tissues will lead to therapeutic failure (see Chapter 93).

In the extremely rare event of infection beneath the deep fascia, muscle may be involved, resulting in another type of episiotomy infection—myonecrosis. Myonecrosis is commonly caused by *Clostridium perfringens,* although it can occur from a neglected necrotizing fasciitis infection that invades the deep fascia and should be considered as a medical emergency. Myonecrosis of the subgluteal muscles surrounding the hip joint or the psoas muscles can also occur from bacteria introduced into this deep space by a paracervical or pudendal needle during the administration of anesthesia. These patients experience severe hip pain associated with marked limitation of motion.

Both myonecrosis and clostridial infection should be treated with surgical resection and antibiotic therapy. For clostridial infection, high-dose penicillin is the therapy of choice. Radical wide excision may be necessary. Hyperbaric oxygen therapy is at best an adjunctive measure to surgical débridement. Polyvalent gas gangrene antitoxin is probably ineffective.

Soper[43] reported an unusually severe form of clostridial myonecrosis arising from an episiotomy caused by *Clostridium sordellii.* The patient had a distinctive course characterized by the sudden onset of severe and unrelenting hypotension associated with marked, generalized tissue edema and third spacing, with increased hematocrit, marked leukemoid reaction, absence of rash or fever, and a rapidly fatal course. This *C. sordellii* toxic shock syndrome was subsequently reported in association with retention of a vaginal pack, degeneration of a cervical myoma, and postpartum endometritis.[44]

Postabortal Infections

Infection after abortion is an ascending process that occurs most commonly in the presence of retained products of conception or operative trauma. Risk factors include greater duration of pregnancy, technical difficulties, and the unsuspected presence of sexually transmitted pathogens or bacterial vaginosis.

Symptoms include fever, chills, abdominal pain, and vaginal bleeding, often with the passage of placental tissue. Postabortal infection typically has its onset within 4 days after the procedure.

Physical findings include an elevated temperature, tachycardia, tachypnea, and abdominal tenderness. In the presence of bacteremia, hypotension and frank shock may occur, and the patient may be agitated or disoriented. Pelvic examination reveals a sanguinopurulent discharge and uterine tenderness, with or without adnexal and parametrial tenderness. It is important to look for cervical or vaginal lacerations, especially with a suspected illegal abortion. Transvaginal ultrasonography can assess the intrauterine cavity for the presence of retained products of conception, suggesting the need for uterine curettage.

Septic abortion caused by *C. perfringens* has a characteristic clinical presentation and can be rapidly fatal. In severe cases massive intravascular hemolysis produces jaundice, mahogany-colored urine, and catastrophic anemia.

Laboratory evaluation of patients with more than early uncomplicated postabortal endometritis should include a complete blood cell count, urinalysis, and culture of the endometrial cavity with an endometrial suction curet; blood cultures; and CT of the abdomen and pelvis and upright chest radiographs looking for a foreign body or intrauterine gas. Simple endometritis, defined as low-grade fever associated with mild uterine tenderness after uncomplicated elective abortion, can be treated with combined parenteral and oral regimens recommended for the treatment of PID (Table 109.1). Patients with established infection, as indicated by fever higher than 38°C (100.4°F), pelvic peritonitis, or tachycardia, should be hospitalized for parenteral antibiotic therapy (Table 109.2) and prompt uterine evacuation if retained products of conception are suspected. Stubblefield and Grimes[45] reviewed the management of these cases.

Surgical removal of any residual infected tissue is essential in all but the mildest of postabortal infections. Pelvic ultrasonography can be used to confirm the presence of retained tissue. In most cases prompt

TABLE 109.1 Recommended Parenteral Regimens

Cefotetan, 2 g IV every 12 h
plus
Doxycycline, 100 mg PO or IV every 12 h
or
Cefoxitin, 2 g IV every 6 h
plus
Doxycycline, 100 mg PO or IV every 12 h
or
Clindamycin, 900 mg IV every 8 h
plus
Gentamicin loading dose, IV or IM (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) every 8. Single daily dosing (3–5 mg/kg) can be substituted.

IM, Intramuscular; *IV,* intravenous; *PO,* oral.
From Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–140.

TABLE 109.2 Intravenous Antibiotic Regimens for Treating Gynecologic Postoperative Infections

Localized Infection With Minimal Systemic Findings

Cefotaxime, 1 g q8h
Cefotetan, 2 g q12h
Cefoxitin, 2 g q6h
Ceftriaxone, 2 g, then 1 g q24h
Ampicillin-sulbactam, 3 g q6h
Ticarcillin-clavulanic acid, 3.1 g q4–6h
Piperacillin-tazobactam, 3.375 g q6h

Extensive Infection With Moderate-to-Severe Systemic Findings

Clindamycin, 900 mg IV q8h
plus
Gentamicin, 2 mg/kg IV, then 1.5 mg/kg q8h (or single daily dose 5 mg/kg)
with or without
Ampicillin, 2 g IV, then 1 g IV q4h
or
Ampicillin, 2 g IV, then 1 g IV q4h
plus
Gentamicin, 2 mg/kg IV, then 1.5 mg/kg q8h (or single daily dose 5 mg/kg)
plus
Metronidazole, 500 mg IV q8h
or
Imipenem-cilastatin, 500–1000 mg IV q6h
or
Meropenem, 1 g IV q8h
or
Ertapenem, 1 g IV q 24h
or
Levofloxacin, 500 mg IV q24h
plus
Metronidazole, 500 mg IV q8h

IV, Intravenous.
From Larsen JW, Hager WD, Livengood CH, et al. Guidelines for the diagnosis, treatment and prevention of postoperative infections. Infect Dis Obstet Gynecol. *2003;11:65–70.*

curettage controls the infection. If the uterus is too large to allow suction curettage, oxytocin or vaginal misoprostol administration is often successful. Concurrent laparoscopy may be needed for curettage of a uterus that was perforated at the time of abortion.

Indications for laparotomy and possible hysterectomy include failure to respond to uterine evacuation and appropriate medical therapy, perforation and infection with suspected bowel injury, pelvic and adnexal abscess, and clostridial necrotizing myonecrosis (gas gangrene). Isolation of *C. perfringens* alone does not mandate hysterectomy. Initial treatment should include high-dose penicillin (5 million units) or ampicillin-sulbactam (3 g) intravenously every 6 hours, curettage, supportive therapy, and intensive cardiovascular monitoring. Laparotomy is indicated, and hysterectomy should be considered if there is deterioration or no response.

Avoidance of unwanted pregnancies by making contraceptives available is the most important preventive measure. Screening for sexually transmitted diseases and bacterial vaginosis before performance of elective abortion is optimal but often impractical. A meta-analysis revealed a substantial protective effect of antibiotic prophylaxis in all subgroups of women undergoing induced abortion, even women in low-risk groups. Routine use of periabortal antibiotics, such as doxycycline, in the United States may prevent up to half of all cases of postabortal infections.[46,47]

Medical abortion with mifepristone (a progesterone antagonist) and misoprostol (a prostaglandin) is commonly used for elective first-trimester terminations. There have now been five reported cases of *C. sordellii* toxic shock syndrome associated with medical abortion. This syndrome is characterized by the rapid onset of profound hypotension, hypothermia, a marked leukemoid reaction, and hemoconcentration. Infection with *C. sordellii* in these cases was associated with lethal toxin production (*C. sordellii* cytotoxin L), thus explaining why the syndrome is uniformly fatal.[48]

SURGICAL SITE INFECTION AFTER GYNECOLOGIC SURGERY

The identification of SSI involves interpretation of clinical and laboratory findings, and it is crucial that surveillance programs use definitions that are consistent and standardized. The SSIs (organ or space) associated with hysterectomy are cuff cellulitis, pelvic cellulitis, and pelvic abscess.

Pathogenesis

Microbial contamination of the surgical site is a necessary precursor of SSI. The risk for SSI can be conceptualized according to the following relationship[49]:

$$\text{Dose of bacterial contamination} \times \text{Virulence} \div \text{Resistance of host patient} = \text{Risk for SSI}$$

Quantitatively, it has been shown that if a surgical site is contaminated with more than 10^5 microorganisms per gram of tissue, the risk for SSI is markedly increased.[50] However, the dose of contaminating microorganisms required to produce infection may be much lower if foreign material is present at the site.[51]

Hysterectomy can be performed as a total vaginal hysterectomy, total abdominal hysterectomy, or laparoscopically assisted vaginal hysterectomy. The latter may also be robotically assisted. For SSIs that occur after hysterectomy performed by any method, the source of pathogens is the endogenous microbiota of the vagina. The normal vaginal microbiota consists of lactobacilli, various species of streptococci, *G. vaginalis,* strains of Enterobacteriaceae, and anaerobes. Although anaerobes predominate numerically (10:1), the concentration of lactobacilli in normal women surpasses that of the anaerobic bacteria by a factor of 100 to 1000.[52] Lactobacilli produce both hydrogen peroxide and lactic acid, which play crucial roles in protecting against the overgrowth of pathogens in the vagina. Pathogenic microorganisms, such as group B streptococci, *E. coli,* and *G. vaginalis,* and anaerobes, such as *P. bivia,* are present in increased concentrations in women without these protective microbiota or equivalent lactic acid–producing taxa (e.g., those with bacterial vaginosis).

Other factors alter the vaginal microbiota and may indirectly predispose to postoperative infection. Ohm and Galask[53,54] showed that *E. coli, Klebsiella, Proteus, Enterobacter, B. fragilis,* and enterococci are more common in 5-day postoperative vaginal cultures after abdominal or vaginal hysterectomy than in preoperative cultures from the same patients. Although several studies have documented increased enterococcal colonization after perioperative cephalosporin prophylaxis, other factors must be involved because placebo-treated groups show increased enterococcal colonization as well.

Once the vaginal epithelium is breached during excision of the cervix, microorganisms gain entry to the vaginal cuff, paravaginal tissues, and peritoneal cavity. The animal model of intraabdominal infection devised by Weinstein and colleagues[55] clarified the distinctive roles played by different bacteria in the natural history of pelvic infection. These investigators documented a biphasic response to infection consisting of an initial phase characterized by peritonitis and sepsis, in which gram-negative aerobic bacteria predominate (peritonitis stage), and a secondary phase with abscess formation, in which anaerobes predominate (abscess stage) (Fig. 109.2).

Risk Factors

Several factors, some of which are beyond the surgeon's control, influence the likelihood of the development of a postoperative infection. Febrile morbidity is more common after abdominal than after vaginal hysterectomy.[56] The incidence of postoperative infection is higher in patients of lower socioeconomic status, regardless of surgical approach. Age has inconsistently been shown to be a risk factor after hysterectomy, with premenopausal women shown to be at increased risk in some studies, especially after vaginal hysterectomy. Duration of surgery is directly correlated with postoperative infection rates.[57]

Bacterial vaginosis has been associated with an increased risk for infection after hysterectomy.[58] Available data suggest it may be prudent for patients scheduled for elective hysterectomy to undergo screening for bacterial vaginosis before the planned procedure. Those found to have bacterial vaginosis should be treated preoperatively or with metronidazole perioperatively for at least 4 days.[59]

Cuff Cellulitis

An inflammatory response at the margins of the vaginal cuff incision is a normal part of the healing process in the early posthysterectomy period. Host defense mechanisms quickly resolve this cellulitis in most patients without the need for antibiotic administration. Hemsell[60] observed that 17% of women undergoing vaginal hysterectomy and 35% of those undergoing abdominal hysterectomy had recurrent temperature elevations on the second or third postoperative day despite normal abdominal and pelvic examinations and no pain. These patients become afebrile without therapy. In a small number of cases, however, cuff cellulitis after hysterectomy requires antibiotic therapy. These women usually present within 10 days after surgery complaining of

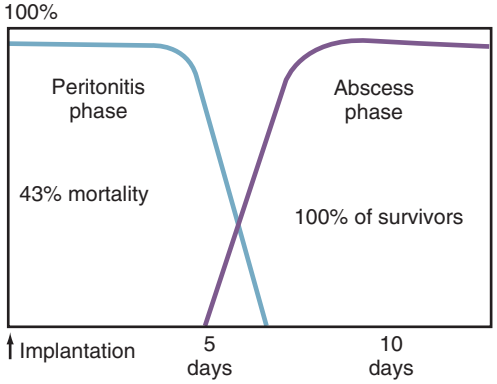

FIG. 109.2 Biphasic pathophysiology of polymicrobial pelvic infection. *(From Weinstein WM, Onderdonk AB, Bartlett JG, et al. Experimental intraabdominal abscesses in rats: development of an experimental model.* Infect Immun. *1974;10:250–1255.)*

increasing central lower abdominal and pelvic pain, increased vaginal discharge, and low-grade fever. Abdominal examination is normal or elicits only slight suprapubic tenderness to deep palpation. On bimanual examination only the vaginal surgical margin is tender, and no masses are palpable. Women with cuff cellulitis have been treated successfully as outpatients with oral antibiotics, but it is important to choose an antibiotic regimen that includes coverage for anaerobic microorganisms. Examples of such regimens include (1) amoxicillin–clavulanic acid or (2) the combination of a first-generation cephalosporin, a quinolone, or trimethoprim-sulfamethoxazole with metronidazole. Patients should monitor their temperatures at home, and clinical reevaluation should be considered if improvement in pain and temperature is not noted by 72 hours.

A well-localized collection of pus just above the vaginal cuff (vaginal cuff abscess) develops in a few patients with cuff cellulitis. In addition to fever, these women may report a sense of fullness in the lower abdomen. Bimanual pelvic examination confirms the presence of a vaginal cuff mass, and ultrasonography can confirm the presence of an abscess. Vaginal drainage facilitates cure and may be accomplished simply by dilation of the vaginal cuff in a treatment room. Some patients with larger collections may benefit from drainage under ultrasonographic or CT guidance by an interventional radiologist or an operative drainage procedure. Any purulent material recovered should be cultured for aerobic and anaerobic pathogens.[61]

Broad-spectrum parenteral antibiotics (see Table 109.2) covering both aerobic and anaerobic bacteria should be given until the patient has been afebrile for 24 to 36 hours. Many experts suggest initiating antibiotic therapy with a single broad-spectrum agent, whereas others recommend combination therapy (e.g., clindamycin plus gentamicin), even for clinically milder infections.[62]

Pelvic Abscess

The most serious late postoperative complication is a pelvic abscess. These abscesses may involve one or both residual adnexa (tubo-ovarian abscess) if the fallopian tubes and ovaries were not removed at surgery.

These infections are rare, occur almost exclusively in premenopausal women, occur despite the use of prophylactic antibiotics, and often have a latent period of many weeks between surgery and onset of symptoms.[63]

Patients may have had no apparent infection during their initial hospitalization, or, alternatively, they may have appeared to respond rapidly to the initial selection of antibiotics for presumed pelvic cellulitis, only to experience relapse after discharge. Typically, the fever curve is characterized by a high spike late in the afternoon or early evening. The leukocyte count is often in the range of 20,000/mm^3, and the erythrocyte sedimentation rate is markedly increased. Patients with postoperative adnexal abscess often have a palpable mass high in the pelvis.[64] Ultrasonography and CT both confirm the presence of a mass and help to determine whether it is loculated, related to an intraperitoneal structure, or drainable percutaneously. Because their location is removed from the vaginal cuff, pelvic/adnexal abscesses cannot be drained through the vaginal cuff unless they extend to the cul-de-sac.

Identification of a postoperative pelvic abscess does not mandate immediate drainage if it is inaccessible because antibiotic therapy alone may be successful in the treatment of this complication. The frequent isolation of a β-lactamase–producing *Prevotella* spp. from these abscesses warrants the use of clindamycin, metronidazole, or other agents effective against gram-negative anaerobes. A regimen of clindamycin plus gentamicin is frequently used. For patients whose infection fails to respond to appropriate antibiotic therapy, drainage is necessary. Ledger and colleagues[65] showed that most such antibiotic failures are caused not by antimicrobial resistance but by the unique environment of the abscess, which inhibits antibiotic effectiveness. Necrosis associated with these types of infections makes surgical exploration necessary in some cases.

If the abscess is located in the posterior cul-de-sac, drainage via colpotomy can be attempted under ultrasonographic guidance. The abscess cavity should be completely evacuated and a drain placed to prevent reaccumulation of fluid. Abscesses not located in the cul-de-sac may be drained percutaneously if they are located adjacent to the abdominal wall or are determined to be accessible by CT. A pigtail or equivalent catheter should remain in place until drainage ceases, usually 4 to 8 days.[66,67] Patients with suspected postoperative pelvic abscess who fail to respond to antibiotic therapy and cannot undergo drainage by one of the previously mentioned techniques require operative laparoscopy or laparotomy. In most cases the adnexa are involved and must be removed. Purulent material or tissue must be submitted for both aerobic and anaerobic culture.

Parenteral antibiotics should be administered until the patient has remained afebrile for 48 to 72 hours, the leukocyte count is normal, and the signs and symptoms have resolved. Most clinicians choose to treat these patients for 7 days after discharge with oral agents, such as amoxicillin-clavulanate or metronidazole. All patients should be reexamined 2 weeks after discharge to ensure that recurrence or reaccumulation of the abscess has not occurred.[68]

Osteomyelitis Pubis

Osteitis pubis has been described as a noninfectious, self-limited inflammatory condition of the symphysis pubis associated with retropubic urologic procedures.[69] It is now recognized that this condition is actually an osteomyelitis of the pubis. It is a rare infection that results from direct inoculation of the bone at the time of surgery or extension of a contiguous focus of infection. Most cases in women occur after urethral suspension or, less commonly, after radical vulvectomy or pelvic exenteration. The diagnosis is based on typical symptoms of suprapubic discomfort, difficulty with ambulation and a wide-based waddling walk, and changes on radiography or magnetic resonance imaging showing irregular bony margins and rarefaction and widening of the symphyseal joint spaces. Wound drainage, low-grade fever, moderate leukocytosis, and an increased erythrocyte sedimentation rate or alkaline phosphatase level may be present.[70]

Patients for whom clinical and radiologic findings are suggestive of this diagnosis should undergo a needle bone biopsy guided by CT.[71] Specimens should be submitted for histopathologic examination and aerobic and anaerobic culture. If pathogenic microorganisms are recovered and if the interval between onset of symptoms and diagnosis is short, a trial of antimicrobial therapy may be attempted. Patients with a poor response to this management should undergo débridement. If pathogenic microorganisms are not isolated from a needle aspirate, open surgical biopsy with débridement should be undertaken, and specimens of bone or purulent material should be cultured. Common isolates include aerobic gram-negative bacteria and staphylococcal and streptococcal species. After débridement directed antimicrobial therapy should be administered for at least 4 weeks.[72]

Sacral osteomyelitis as a complication of abdominal sacral colpopexy has been reported.[73]

PELVIC INFLAMMATORY DISEASE

PID refers to the clinical syndrome that represents a continuum of inflammation from the cervix to the endometrium, fallopian tubes, and contiguous pelvic structures: cervicitis, endometritis, salpingitis, pelvic peritonitis, and tubo-ovarian abscess.[74,75] Each year, approximately 1 million women in the United States experience an episode of symptomatic PID. Many women with PID have minimal or no symptoms.[76]

PID results from direct canalicular spread of microorganisms from the vagina or endocervix to the endometrium and fallopian tube mucosa.[77] Both *Neisseria gonorrhoeae* and *C. trachomatis* commonly cause endocervitis, and clinical symptoms of acute PID develop in 10% to 40% of women with these infections who do not receive adequate treatment.[78] In addition to *N. gonorrhoeae* and *C. trachomatis,* a wide variety of bacteria have been isolated from the upper genital tracts of women with acute, symptomatic PID, including anaerobes, gram-negative rods, streptococci, and mycoplasmas.[79,80] Many of these are the same microorganisms that are found in increased concentrations in the vagina of women with bacterial vaginosis.[81] Moreover, approximately one of every four women with presumed uncomplicated lower genital tract gonococcal or chlamydial infection is found to have histologic endometritis (subclinical PID) when evaluated by endometrial biopsy.[77] Uncommonly, respiratory pathogens, including *Haemophilus influenzae, Streptococcus pyogenes*, and *Histoplasma capsulatum* have also been isolated from the upper genital tracts of women with symptomatic PID.[82–84]

Risk Factors

Age is inversely related to the rate of PID. Sexually experienced teenagers are three times more likely to be diagnosed with PID than are women 25 to 29 years of age. A history of multiple sexual partners, an increased rate of acquisition of new partners within the previous 30 days, and frequent sexual intercourse with a single partner are all associated with an increased risk for PID.[85] Women with confirmed PID commonly have concurrent bacterial vaginosis.[86] Contraceptive choice modifies PID risk in a complex manner. Mechanical and chemical barriers decrease risk. Oral contraceptives have a variable effect, decreasing the risk for a clinical diagnosis of PID but having no effect on the rate of infertility or endometrial inflammation. Intrauterine contraceptive devices (IUDs) confer a slightly increased risk for non–sexually transmitted PID in the first month after insertion.[87] Other suggested associations with PID include douching, menses, cigarette smoking, and substance abuse.[88,89]

The improved IUDs—the levonorgestrel intrauterine system and the copper intrauterine device—are rarely associated with infection. Contamination of the endometrial cavity at insertion apparently results in a slightly increased risk for acute PID that is limited to the first 4 months of IUD use. Infections occurring after 4 months are believed to be the result of acquired sexually transmitted pathogens and not the IUD itself.[90]

A unique role for *Actinomyces* organisms in IUD-associated PID has been suggested, but this relationship remains unclear. Although as many as 4% to 8% of IUD users have *Actinomyces*-like organisms identified on Papanicolaou (Pap) smear, their presence has not been equated with pelvic actinomycosis, nor has the risk for subsequent pelvic infection been quantified.[91] In patients with cytology showing *Actinomyces* colonization, Lippes[92] showed that removal of the IUD was not necessary.

Diagnosis

The clinical diagnosis of acute PID is imprecise. Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value of 65% to 90% compared with laparoscopy. The positive predictive value of a clinical diagnosis of acute PID varies depending on epidemiologic characteristics and the clinical setting, with a higher positive predictive value among sexually active young women (particularly adolescents), among patients attending sexually transmitted diseases clinics, and in settings in which the rates of gonorrhea, chlamydia, and bacterial vaginosis are high.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are underdiagnosed because the patient or the health care provider fails to recognize the implications of mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, vaginal discharge). In one study chlamydial infection was noted in 29% of women experiencing persistent intermenstrual bleeding while taking oral contraceptives, suggesting the presence of endometritis.[93] Given the often subtle presentation of this disease and the significant reproductive sequelae associated with it (infertility, ectopic pregnancy, chronic pelvic pain), clinicians should maintain a low threshold for the diagnosis of PID.

Empirical treatment for PID should be considered in sexually active young women and other women at risk for sexually transmitted infections if the following minimum criteria are met and no other cause for the illness can be identified: (1) pelvic organ tenderness noted on bimanual examination with or without manipulation of the cervix and (2) microscopy showing the presence of WBCs in the vaginal secretions. Most women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of the vaginal secretions (Fig. 109.3). If cervical discharge appears normal and no WBCs are found during microscopy, the diagnosis of PID is unlikely and alternative causes of pain should be investigated.[94] Additional criteria that support a diagnosis of PID include bacterial vaginosis, mucopurulent cervicitis, laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis,* oral temperature higher than 38°C (100.4°F), and elevated erythrocyte sedimentation rate or C-reactive protein level. Definitive criteria for PID include histologic evidence of endometritis on endometrial biopsy; transvaginal ultrasonography or other imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex; and laparoscopic abnormalities showing tubal purulent exudate, erythema, and edema (Fig. 109.4).

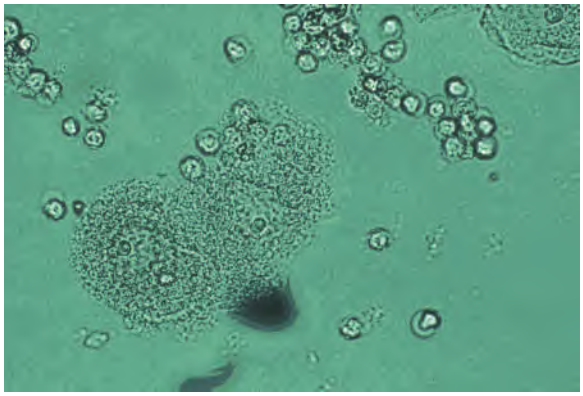

FIG. 109.3 Microscopy of a wet mount of the vaginal secretions reveals clue cells and inflammatory cells in a patient with pelvic inflammatory disease (×400).

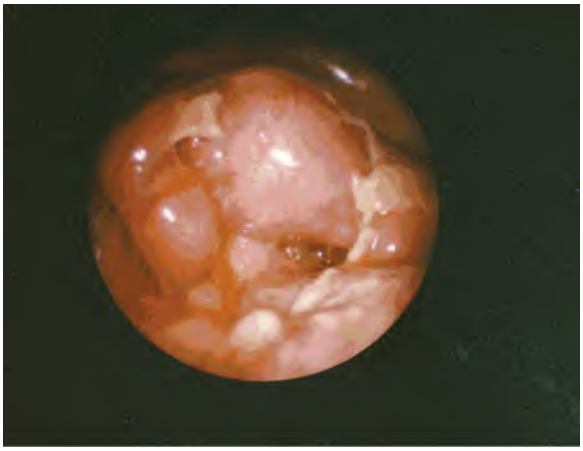

FIG. 109.4 Laparoscopic confirmation of moderate acute salpingitis showing patchy fibrin deposits on the serosal surfaces of the fallopian tubes. *(From Soper DE. Cervicitis and endometritis. In: Mandell GL, Sobel JD, eds.* Atlas of Infectious Diseases. *Vol. 9. Philadelphia: Churchill Livingstone; 1997:810.)*

Clinical diagnosis and grading of PID have poor specificity. In fact, women with PID associated with moderate-to-severe pelvic adhesions or tubal occlusion were found to have less tenderness on abdominopelvic examination and therefore to appear less ill than women with limited or no adhesions.[95] Diagnostic laparoscopy should be considered in patients for whom empirical therapy has failed and in patients with a history of recurrent PID and negative tests for chlamydia, gonorrhea, and bacterial vaginosis. Endometriosis is a common alternative diagnosis in these women.

Although rare, acute salpingitis can occur in the proximal stump of patients who have undergone surgical sterilization and in women in the first trimester of pregnancy.

Management of Acute Pelvic Inflammatory Disease

Most women with PID are treated as outpatients, reflecting the preponderance of patients with only mild-to-moderate symptoms and signs. A prospective, randomized clinical trial compared outpatient treatment with a single dose of cefoxitin intramuscularly and multidose oral doxycycline with inpatient treatment with intravenous cefoxitin and doxycycline in women with clinical symptoms and signs of mild-to-moderate PID. There were no differences in response to therapy or reproductive outcome between inpatient and outpatient regimens.[96] These data suggest that

hospitalization can be reserved for those patients with clinically severe disease (severe illness, nausea and vomiting, or high fever), those unable to follow or tolerate an outpatient oral regimen, pregnant women, and women with a clinical diagnosis of tubo-ovarian abscess.

Treatment consists of pelvic rest and antibiotics. Antibiotic regimens must provide empirical, broad-spectrum coverage of likely pathogens, including *N. gonorrhoeae, C. trachomatis,* anaerobes, gram-negative facultative bacteria, and streptococci. Several antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up. The need to eradicate anaerobes from women with PID has not been determined definitively. However, anaerobic bacteria associated with bacterial vaginosis have been isolated from the upper reproductive tract of women with PID, and these bacteria have been shown to cause tubal and epithelial destruction. One method of determining the appropriateness of metronidazole therapy in women with PID is to determine the presence of concurrent bacterial vaginosis. Metronidazole should be prescribed for women with the clinical diagnosis of PID and concurrent bacterial vaginosis.

The fluoroquinolones alone are no longer recommended in the treatment of PID due to the emergence of quinolone-resistant *N. gonorrhoeae*. The CDC has updated the published antibiotic treatment guidelines for acute PID (see Table 109.1, Table 109.3).[97] If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin, 500 mg PO once daily, or ofloxacin, 400 mg twice daily for 14 days) usually with metronidazole (500 mg PO twice daily for 14 days) may be considered if the community prevalence and individual risk for gonorrhea is low. Tests for gonorrhea must be performed before instituting therapy. If the nucleic acid amplification test result is positive for gonorrhea, a parenteral cephalosporin is recommended. If culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility. If the isolate is quinolone-resistant *N. gonorrhoeae* or if antimicrobial susceptibility cannot be assessed, parenteral cephalosporin is recommended, and/or consultation with an infectious disease expert is indicated in case of cephalosporin allergy. Although information regarding other outpatient regimens is limited, amoxicillin-clavulanic acid and doxycycline or azithromycin with metronidazole have demonstrated short-term clinical cure.[98]

Optimal outpatient management includes a follow-up examination performed within 72 hours after the initiation of therapy. Many patients may not return for this visit if they are symptomatically improved. Substantial clinical improvement with lysis of fever, reduction in direct or rebound abdominal tenderness, and reduction in pelvic organ tenderness with bimanual examination should be noted. If there is no response to therapy within 72 hours, patients should be reevaluated and possibly hospitalized for a potential diagnostic/therapeutic laparoscopy to confirm the diagnosis and for consideration of parenteral antibiotic therapy if they are on an oral regimen.

All male sex partners of women with acute PID should be evaluated for sexually transmitted diseases, and those who had sexual contact with the patient during the 60 days preceding the onset of symptoms in the patient should be empirically treated with regimens effective against *C. trachomatis* and *N. gonorrhoeae*. In many circumstances the male sex partner tests positive for chlamydia or gonorrhea, but the patient receiving therapy is negative, suggesting a sexually transmitted etiology and a false-negative test in the woman with PID.[99]

TABLE 109.3 Recommended Intramuscular/ Oral Regimens

Ceftriaxone, 250 mg IM in a single dose
plus
Doxycycline, 100 mg PO twice a day for 14 days
with[a] *or without*
Metronidazole, 500 mg PO twice a day for 14 days
or
Cefoxitin, 2 g IM in a single dose and Probenecid, 1 g PO administered concurrently in a single dose
plus
Doxycycline, 100 mg PO twice a day for 14 days
with or without
Metronidazole, 500 mg PO twice a day for 14 days
or
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
plus
Doxycycline, 100 mg PO twice a day for 14 days
with[a] *or without*
Metronidazole, 500 mg PO twice a day for 14 days

[a]The recommended third-generation cephalosporins are limited in the coverage of anaerobes. Therefore, until it is known that extended anaerobic coverage is not important for treatment of acute PID, the addition of metronidazole to treatment regiments with third-generation cephalosporins should be considered.
IM, Intramuscular; *PID,* pelvic inflammatory disease; *PO,* oral.
From Walker CK, Wiesenfeld HC. Antibiotic therapy for acute pelvic inflammatory disease: the 2006 CDC Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis. *2007;28(suppl 1):S29–S36.*

Management of Suspected Tubo-ovarian Abscess

Patients with suspected tubo-ovarian abscess should be hospitalized and given broad-spectrum antimicrobial drugs that include adequate coverage for gram-negative anaerobes. Failure to respond to medical therapy is suggested by a lack of defervescence within 72 hours or an increase in the size of the mass. Eighty-five percent of abscesses with a diameter of 4 to 6 cm respond to antibiotics alone, but only 40% of those 10 cm or larger respond.[100] Triple-agent therapy with ampicillin, clindamycin, and gentamicin would seem to be the regimen of choice, although other combination regimens have been used effectively.[100,101]

Surgical intervention for a tubo-ovarian abscess that does not respond to antimicrobial therapy can be performed laparoscopically, percutaneously, or transvaginally or by laparotomy. A patient with a suspected leaking or ruptured abscess should undergo immediate surgical exploration after rapid stabilization and institution of broad-spectrum antibiotics due to a nonnegligible rate of mortality associated with this clinical scenario.[102]

Sequelae

After one episode of PID a woman's risk for ectopic pregnancy increases sevenfold. Approximately 13% of women are infertile after a single episode of PID, 25% to 35% after two episodes, and 50% to 75% after three or more episodes. If a true tubo-ovarian abscess is present, only 7% to 14% of patients are able to conceive after treatment. After treatment for a tubo-ovarian complex (a less-restrictive diagnostic category than tubo-ovarian abscess), approximately two-thirds of women attempting pregnancy are unable to conceive. Other sequelae associated with PID include dyspareunia, pelvic adhesions, and chronic pelvic pain.[103] One study has suggested that screening for and treatment of cervical chlamydial infection can prevent greater than 50% of PID in a given locale.[104]

ACKNOWLEDGMENT

The author and the editors of *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (PPID) recognize the dedication and many contributions of Dr. David Soper to this field over many years, and his work on this chapter in the prior editions of PPID.

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110 Prostatitis, Epididymitis, and Orchitis

Catherine C. McGowan

SHORT VIEW SUMMARY

Definitions and Classification
- For the National Institutes of Health classification of prostatitis syndromes, see Table 110.2.
- Acute bacterial prostatitis is associated with lower urinary tract infection and sepsis.
- Chronic bacterial prostatitis is associated with recurrent lower urinary tract infections caused by the same bacterial clade.
- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) occurs in absence of uropathogenic bacteria.
- Acute epididymitis and orchitis are usually due to infectious agents or local trauma.

Epidemiology
- Prostatitis represents the most common urologic diagnosis in healthy young men. Fifty percent of men may experience symptoms in their lifetimes. Prevalence is 2% to 16%.
- Nearly 90% of men evaluated for genitourinary symptoms have CP/CPPS.
- Sexually transmitted epididymitis is most common in young men, whereas infection with coliform organisms is the most common cause of epididymitis in men older than age 35. Men with bacterial epididymitis may have underlying urologic pathology or recent genitourinary tract manipulation.
- Isolated orchitis is rare.

Microbiology
- Gram-negative Enterobacteriaceae cause most episodes of bacterial prostatitis. Enterococci account for a small percentage.
- Etiology of epididymitis and orchitis reflects patient age. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* predominate in young men, and coliform or *Pseudomonas* species predominate in older men.
- Most orchitis is caused by viral infections.

Diagnosis
- Careful history, physical examination, urinalysis, and urine culture are essential.
- The lower urinary tract localization test (see Table 110.1) is the gold standard.
- Epididymitis and orchitis should be evaluated with urine or urethral nucleic acid amplification testing for *C. trachomatis* and *N. gonorrhoeae*. A urethral smear for Gram stain and a midstream urine culture are useful for establishing other etiologies.

Therapy
- Fluoroquinolones are preferred oral treatment for prostatitis. Quinolone resistance is increasingly common, especially in infections occurring after genitourinary tract instrumentation.
- Septic patients should receive empirical broad-spectrum parenteral therapy.
- Combinations of antibiotics, α-blockers, antiinflammatory agents, and pain management therapies represent the most effective treatment for CP/CPPS.
- Combination therapy with intramuscular ceftriaxone plus either azithromycin or doxycycline is recommended for *N. gonorrhoeae* infections.

ANATOMY AND PHYSIOLOGY OF THE TESTES AND MALE ACCESSORY SEX ORGANS

The testicle has two functional components: seminiferous tubules and interstitial cells. Sperm production is the primary function of the seminiferous tubules. Interstitial cells, located between the seminiferous tubules, produce sex hormones. After spermatogenesis, spermatozoa are transported from the testis into the epididymis (Fig. 110.1). Sperm move into the vas deferens, a muscular tube approximately 12 inches long that is easily palpable in the scrotum. Fructose from the seminal vesicles is the major energy source for ejaculated sperm. In addition, the seminal vesicles provide proteins that coagulate the ejaculate. Liquefaction of the semen occurs 5 to 30 minutes after ejaculation because of proteolytic enzymes from the prostate.

HOST DEFENSES OF THE MALE LOWER UROGENITAL TRACT

Organisms that ascend through the urethra cause most infections of the urogenital ducts and accessory sex organs. Mechanical factors, such as the flushing action of micturition and ejaculation, should provide some protection against infection, although the relative significance of these defenses is unclear.

A zinc-containing polypeptide termed the *prostatic antibacterial factor* is the most important antimicrobial substance secreted by the prostate.[1] Men with chronic prostatitis have significantly lower levels of zinc in their prostatic fluid than healthy men, despite normal serum zinc levels.[1,2] Other findings suggest that bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are associated with prostatic secretory dysfunction.[3] It is unclear whether reduced zinc concentrations precede the development of prostatic infection or result from secretory dysfunction. Prostatic secretions from patients with bacterial prostatitis contain high concentrations of immunoglobulins.[4] Several studies have shown antigen-specific antibody coating of bacteria isolated from the lower urinary tracts of patients with prostatitis.[5] The antigen-specific antibody response in prostatic secretions, predominantly secretory immunoglobulin A, is significantly greater in magnitude than the serologic response. Studies have documented that patients with prostatitis syndromes have high concentrations of cytokines and chemokines in their prostatic secretions and semen.[6,7] Although the precise mechanisms are unclear, local cytokines, chemokines, and other growth factors may contribute to the apparent increased risk of both prostate cancer and symptomatic benign prostatic hypertrophy in men with a history of prostatitis.[8–11]

The presence of leukocytes is characteristic of many inflammatory conditions of the male lower urinary tract, including prostatitis. Phagocytosis of abnormal sperm by leukocytes has been observed in infertile men with pyospermia, but the precise role and significance of prostatic fluid leukocytes is uncertain. Patients with symptoms of prostatitis have more lower urinary tract leukocytes than controls,[12] but no evidence has linked prostatitis symptoms with prostatic fluid leukocyte counts or shown that symptomatic patients with leukocytes in their prostatic secretions respond differently to treatment than symptomatic patients without inflammation.[13]

PROSTATITIS

Classification

The term *prostatitis* has been used clinically to describe various complaints referable to the lower urogenital tract and perineum in men. It has been

estimated that 50% of men experience symptoms of prostatitis at some time in their lives. Studies have suggested that the prevalence of prostatitis is 2% to 16%.[14] In otherwise healthy young men, prostatitis may be the most common urologic diagnosis. A national survey of physician visits found that there were almost 2 million visits annually for prostatitis, accounting for 8% of visits to urologists and 1% of visits to primary care physicians in the United States.[15] In the United States, the direct cost for the diagnosis and management of prostatitis was approximately $84 million in 2000, exclusive of pharmaceutical spending.[16]

The crucial clinical issue is to distinguish patients with lower urinary tract complaints associated with bacteriuria (i.e., patients who may have acute or chronic bacterial prostatitis) from the larger number of patients without bacteriuria. Further classification of patients with prostatitis depends on careful bacteriologic assessment of the lower urinary tract, which is based on sequential cultures obtained during micturition (Table 110.1). Prostatitis syndromes may be classified into four major groups: acute bacterial prostatitis, chronic bacterial prostatitis, CP/CPPS, and asymptomatic inflammatory prostatitis (Table 110.2).[17] In addition, rare patients develop granulomatous prostatitis.

Bacterial prostatitis is a common diagnosis in clinical practice, but well-documented bacterial infections of the prostate, whether acute or chronic, are uncommon. Most patients with a diagnosis of prostatitis are men with perineal, lower back, or lower abdominal pain or ejaculatory complaints. Most patients have no history of bacteriuria and little objective evidence of bacterial infection of the prostate. Patients with symptoms of prostatitis but no evidence of bacteriuria may be classified as having CP/CPPS, but as yet there are few firm data on which to base therapeutic decisions.

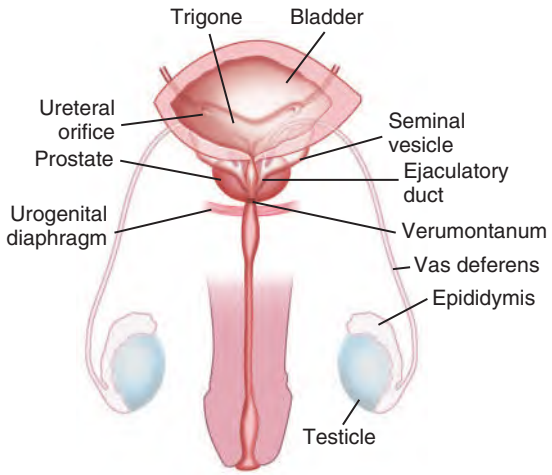

FIG. 110.1 **Anatomy of the male sex organs and lower urinary tract.**

Acute Bacterial Prostatitis

Acute bacterial prostatitis is seldom a subtle or difficult diagnosis. Patients complain of abrupt onset of symptoms associated with lower urinary tract infection, such as urinary frequency and dysuria. Acute edema of the prostate may lead to lower urinary tract obstruction. Signs of systemic toxicity are common. Some such patients have had recent genitourinary tract procedures.[18–20] On physical examination, patients may have fever and lower abdominal or suprapubic tenderness. Findings on rectal examination are frequently impressive, with an exquisitely tender, tense prostate on palpation. Urinalysis is abnormal, with pyuria, and urine culture is positive unless the patient has received prior antimicrobial therapy. Bacteremia may occur spontaneously or may result from excessively vigorous rectal examination. Gram-negative uropathogens, especially *Escherichia coli,* are the causative agents in more than 60% of cases, although infection may be due to *Pseudomonas aeruginosa* and *Enterococcus* species.[19,20] *Escherichia coli* isolates that cause acute prostatitis in healthy young men have been shown to possess specialized urovirulence factors, especially hemolysin and cytotoxic necrotizing factor, with many strains exhibiting multiple virulence factors.[21,22] The isolation of *Staphylococcus aureus* from prostatic secretions or urine should prompt a search for a remote or endovascular source of *S. aureus* infection.

Results of antimicrobial therapy for acute bacterial prostatitis often are dramatic. Many drugs that do not penetrate into the prostate under normal conditions are effective in acute bacterial prostatitis.[23] A variety of antibiotics are appropriate for treating acute bacterial prostatitis, and recommendations for empirical therapy are based on the likelihood of the infecting organism and regional patterns of antimicrobial resistance.

TABLE 110.1 Lower Urinary Tract Localization Using Sequential Urine Cultures

SPECIMEN	SYMBOL	DESCRIPTION
Voided bladder 1	VB_1	Initial 5–10 mL of urinary stream
Voided bladder 2	VB_2	Midstream specimen
Expressed prostatic secretions	EPS	Secretions expressed from prostate by digital massage
Voided bladder 3	VB_3	First 5–10 mL of urinary stream immediately after prostatic massage

[a]Unequivocal diagnosis of bacterial prostatitis requires that the colony count in the VB_3 specimen greatly exceed the count in the VB_1 specimen, preferably by at least 10-fold. Many patients who have chronic bacterial prostatitis harbor only small numbers of bacteria in the prostate. In these patients, direct culture of prostatic secretions is particularly useful. Microscopic examination of the EPS is useful for identifying white blood cells and oval fat bodies (large lipid-laden macrophages characteristic of the prostatic inflammatory response).
From Stamey T. Pathogenesis and Treatment of Urinary Tract Infections. *Baltimore: Williams & Wilkins; 1980.*

TABLE 110.2 Classification of Prostatitis Syndromes on the Basis of Lower Urinary Tract Localization Studies

CONDITION	BACTERIURIA[a]	INFECTION LOCALIZED TO PROSTATE[b]	INFLAMMATORY RESPONSE[c]	ABNORMAL RECTAL EXAMINATION OF PROSTATE[d]	SYSTEMIC ILLNESS[e]
Acute bacterial prostatitis	+	+	+	+	+
Chronic bacterial prostatitis	+	+	+	–	–
Chronic prostatitis/chronic pelvic pain syndrome					–
Inflammatory subtype[f]	–	–	+	–	–
Noninflammatory subtype[g]	–	–	–	–	–
Asymptomatic inflammatory prostatitis	–	–	+	±	–

[a]Documented with an identical organism that is shown to localize to a prostatic focus when the midstream urine culture is negative.
[b]See text for diagnostic criteria.
[c]In expressed prostatic secretions, semen, postmassage urine, or prostate tissue.
[d]Abnormal findings include exquisite tenderness and swelling that may be associated with signs of lower urinary tract obstruction.
[e]Systemic findings frequently include fever and rigors and may include signs of bacteremia.
[f]Formerly termed *nonbacterial prostatitis.*
[g]Formerly termed *prostatodynia.*
From Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. *1999;282:236–237.*

In most settings, fluoroquinolones or trimethoprim-sulfamethoxazole are the preferred oral agents, due to their superior penetration into the prostate. However, quinolone resistance is increasingly common, especially in patients who develop bacterial prostatitis after genitourinary instrumentation. Nearly 90% of *E. coli* isolates were resistant to fluoroquinolones in several studies of acute prostatitis occurring after prostate biopsy.[24,25] Systemically ill patients should receive empirical parenteral therapy with a third-generation cephalosporin or a carbapenem, possibly combined with an aminoglycoside, with subsequent modification based on culture and sensitivity results. Severe sepsis after manipulation of the genitourinary tract, such as biopsy of the prostate, may be caused by *E. coli* strains that are multidrug-resistant (MDR) to common empirically used antibiotic agents.[26,27] There are limited data regarding duration of antibiotic therapy, and recommendations range from 2 to 4 weeks depending on the severity of illness. Confirmatory urine culture to ensure bacteriologic cure should be done following antibiotic completion.

Urinary retention is managed best with a suprapubic cystostomy, rather than a transurethral catheter, to avoid obstructing drainage of infected prostatic secretions into the urethra. General measures, including hydration, analgesics, and bed rest, also are indicated. The most important complications of acute bacterial prostatitis are prostatic abscess, prostatic infarction, and chronic bacterial prostatitis. Nonspecific granulomatous prostatitis may follow acute lower urinary tract infections and mimic prostate cancer both clinically and histologically.[28,29]

Chronic Bacterial Prostatitis

Chronic bacterial prostatitis is an important cause of bacterial persistence in the male lower urinary tract. Characteristically, patients experience recurrent bacterial urinary tract infections caused by the same organism.[17] Patients often are asymptomatic between episodes of bladder bacteriuria. The prostate gland is usually normal on rectal or endoscopic evaluation. Careful lower urinary tract localization studies constitute the cornerstone on which to base a diagnosis of chronic bacterial prostatitis (see Tables 110.1 and 110.2). Evaluation of pre–prostate massage and post–prostate massage samples has been proposed as an alternative to the traditional lower urinary tract localization study.[30,31] Diagnosis of chronic bacterial prostatitis based solely on symptoms, the number of leukocytes in expressed prostatic secretions, or the use of prostate biopsy specimens is inadequate.

Gram-negative rods (members of Enterobacteriaceae or pseudomonads) are the most important pathogens in chronic bacterial prostatitis. Enterococci may be the causative organisms in some cases. An etiologic role for other gram-positive cocci, such as *S. aureus,* has been suggested.[32] However, studies have demonstrated that repetitive cultures to consistently localize gram-positive bacteria in prostate-specific specimens, such as expressed prostatic secretions, are seldom reproducible in untreated patients, leading to uncertainty regarding the clinical significance of these organisms.[33]

The risk factors for the development of chronic bacterial prostatitis have not been clearly defined. Bacteria isolated from patients with chronic bacterial prostatitis, even after multiple episodes of symptomatic bacteriuria and prolonged antibiotic courses, are often antibiotic-sensitive strains. Several factors may increase the risk of failure of antibiotic therapy in some patients, including poor drug penetration into the prostatic parenchyma, bacterial biofilm formation,[34] prostatic fluid pH changes associated with infection, infected calculi that may serve as persistent foci for bacteria,[35] and incomplete medication adherence. In a retrospective review of 480 patients with acute prostatitis, factors significantly associated with progression to chronic prostatitis in 49 men (10%) were diabetes, prior manipulation, not doing cystostomy, and urethral catheterization.[36]

Depending on the results of antimicrobial sensitivity, the preferred therapy is at least 4 to 6 weeks with an oral fluoroquinolone, which results in microbiologic cure rates of 70% or more.[37,38] Treatment options for prostatitis due to emerging MDR gram-negative bacteria have been limited. Oral fosfomycin, which achieves therapeutic levels in prostatic tissue, has been reported to successfully eradicate infection with MDR *E. coli.*[39] Long-term follow-up with repeated microbiologic evaluation is needed to ensure that patients respond to treatment. Patients with chronic bacterial prostatitis who are not cured may be rendered asymptomatic by long-term suppressive treatment, based on anecdotal clinical experience. Because patients usually are asymptomatic between episodes of bacteriuria, the goal of suppressive therapy is to prevent symptomatic episodes despite the persistence of bacteria in the prostate.

Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Men with CP/CPPS are the largest population with prostatitis, representing more than 90% of patients evaluated. CP/CPPS causes significant morbidity and substantially decreases patients' quality of life.[11,40] Patients may complain of various perineal and pelvic symptoms, especially pain, that may be perineal, suprapubic, infrapubic, penile, scrotal, or inguinal in location and are described as either continuous or spasmodic, and commonly as a "dull ache."[41] Other complaints include voiding difficulty, urinary symptoms, and sexual dysfunction.[42] Systemic symptoms or signs are usually absent, and physical examination generally is unremarkable.

The diagnosis of CP/CPPS is one of exclusion. Patients have no history of bacteriuria and lack objective evidence of bacterial infection of their prostatic secretions on careful lower urinary tract localization studies (see Table 110.2). Some patients with CP/CPPS have leukocytes in expressed prostatic secretions, post–prostate massage urine (voided bladder 3 [VB_3]; see Table 110.1), or semen (in the inflammatory subtype, formerly termed *nonbacterial prostatitis*), whereas others have no objective evidence of inflammation (in the noninflammatory subtype, formerly termed *prostatodynia;* see Table 110.2).[17]

The causes of CP/CPPS are uncertain and subject to ongoing multicenter investigations. Although numerous studies have found no strong evidence for a causative infectious agent,[43–45] others have reported various atypical pathogens in men with CP/CPPS.[46,47] A large prospective study of men with chronic prostatitis found that 74% had an infectious etiology implicated, including *Chlamydia trachomatis* in 37% of cases, *Trichomonas vaginalis* in 11%, *Ureaplasma urealyticum* in 5%, and classic bacterial uropathogens in 20%.[48] The methods, techniques, and control groups used in these various studies have differed considerably. Molecular studies have shown that patients with inflammatory CP/CPPS are significantly more likely to have bacterial DNA in prostatic secretions than patients without inflammation[49] or control patients with prostate cancer.[50] However, other studies have not found bacterial DNA in prostate tissue of patients with moderate to severe symptoms of CPPS.[51]

Many authorities have proposed that CP/CPPS is not an infectious disease, and that multiple extraprostatic factors may be important in the cause of this syndrome. Increased prostaglandins, autoimmunity, psychological abnormalities, neuromuscular dysfunction of the bladder neck or urogenital diaphragm, allergy to environmental agents, and nerve growth factor (a neurotrophin found to have a role in the regulation of nociceptive nerves and as a mediator and amplifier of neurogenic inflammation) all have been suggested as causative factors.[52,53]

Current therapy for symptomatic patients with CP/CPPS is unsatisfactory. The most commonly used modalities include empirical antimicrobial therapy,[54] α-blockers,[55] antiinflammatory therapy,[56] and pain management therapies.[57] A meta-analysis including 23 randomized trials of patients with CP/CPPS found that α-blockers (terazosin, tamsulosin), antibiotics (fluoroquinolones), and combinations of these therapies appeared to achieve the greatest improvement in clinical symptom scores compared with placebo.[58] However, the small statistically significant overall benefit observed may or may not be clinically significant for individual patients, and antimicrobial therapy generally is not recommended as a primary therapy, particularly in patients who have previously failed treatment with antibiotics.[59] One recent double-blind, placebo-controlled study of 60 patients found that transurethral intraprostatic injection of botulinum toxin type A decreased pain scores at 1, 3, and 6 months.[60] Experts recommend conservative therapies such as diet modification, low-impact exercise, local heat therapy, and development of personal coping skills based on their proven worth in clinical practice and with other pain syndromes.[61] More effective treatment of CP/CPPS is the focus of major research efforts. Ongoing National Institutes of Health (NIH)–funded research is focused on patient phenotyping to identify genetic, environmental, and clinical factors (e.g., associated nonurologic conditions, irritable bowel syndrome, chronic widespread pain, etc.), as well as

evidence of "central nervous system sensitization" that may be associated with the likelihood that individual patients will respond to specific therapies.[62]

Asymptomatic Inflammatory Prostatitis

The NIH consensus classification of prostatitis includes a category for patients who have a diagnosis of prostatitis determined by the presence of significant leukocytes (or bacteria or both) in prostate-specific specimens but who have no genitourinary tract symptoms.[17] These patients have prostate inflammation but have none of the usual symptoms associated with other prostatitis syndromes. It is common for patients with elevated prostate-specific antigen levels to undergo prostate biopsy for evaluation of possible prostate cancer. The most common benign pathologic diagnosis is prostatitis, based on the histologic finding of inflammatory infiltrates in the prostatic parenchyma. Some clinicians recommend a course of antimicrobial or antiinflammatory therapy in this situation.[38] These recommendations are based on the observations that acute bacterial prostatitis and exacerbations of chronic bacterial prostatitis are associated with elevations of serum prostate-specific antigen and acid phosphatase levels.[63] Whether antimicrobial therapy is beneficial for asymptomatic patients with histologic evidence of prostatitis is uncertain. The current consensus is that antimicrobial therapy is not indicated for asymptomatic patients.[64]

Histologic evidence of prostatic inflammation also may be noted in patients with no clinical history of prostatitis who have benign prostate tissue removed during surgical procedures for the treatment of bladder outflow obstruction[10] or who have radical prostatectomy for prostate cancer.[65] Inflammatory prostatitis may be diagnosed among asymptomatic men undergoing evaluation for infertility. On semen microscopic analysis, increased numbers of round cells, which could represent immature spermatozoa or white blood cells, may prompt a diagnosis of prostatitis. Other terms used in the infertility literature include *asymptomatic male genital tract infection, male accessory gland infection, prostatoseminal vesiculitis, leukocytospermia,* and *pyosemia* (*pyospermia*). Some specialists recommend antimicrobial therapy, but the proportion of these patients who have active genital tract infections is poorly defined. It would seem prudent to identify a specific genitourinary tract pathogen before recommending antimicrobial therapy for asymptomatic men who present for infertility evaluation.

Epidemiologic studies and other lines of evidence have suggested that prostatitis may be associated with an increased risk for later development of benign prostatic hypertrophy–associated events and with prostate cancer.[8,11,66,67] If these potential associations were confirmed, that would support efforts to diagnose and treat symptomatic and asymptomatic prostatitis syndromes.[65,67] However, at present, such associations are not confirmed.

Granulomatous Prostatitis

Granulomatous prostatitis is a characteristic histologic reaction of the prostate to various insults, with granulomas containing lipid-laden histiocytes, plasma cells, and scattered giant cells. In most cases, granulomatous prostatitis follows an episode of acute bacterial prostatitis.[28] There also are many specific infectious causes of granulomatous reaction by the prostate. Tuberculous prostatitis usually is secondary to tuberculosis elsewhere in the genital tract.[68] Most patients have no symptoms referable to prostatic infection. At biopsy, the granulomas may contain typical Langerhans giant cells and exhibit caseous necrosis. These infections are caused most often by *Mycobacterium tuberculosis* but also have been reported with nontuberculous mycobacteria. Iatrogenic mycobacterial prostatitis may develop in patients who receive intravesicular bacille Calmette-Guérin for treatment of transitional cell carcinoma of the bladder.[69] Prostatitis may be secondary to systemic infection with many of the deep mycoses.[70] Most cases of fungal prostatitis reported have been associated with blastomycosis, coccidioidomycosis, and cryptococcosis.[71,72] The prostate may be a focus of persistent cryptococcosis in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Rarely, prostatic histoplasmosis occurs in these patients.[73]

Granulomatous prostatitis is most important in the differential diagnosis for an indurated, firm, or nodular prostate. Findings on rectal examination in these patients raise the suspicion of prostatic carcinoma. Biopsy usually is necessary for diagnosis, and it is important that appropriate stains and cultures be used to detect specific causative agents.

FIG. 110.2 Computed tomography scan of a prostatic abscess lateral to the urethra *(arrow).* *(From Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, Dolan R, eds.* Principles and Practice of Infectious Diseases. *6th ed. Philadelphia: Churchill Livingstone; 2005:894.)*

Prostatic Abscess

Prostatic abscess is a rare complication of prostatitis in the antibiotic era.[74] Most prostatic abscesses occur in patients with diabetes or with an immunocompromised state and in patients who have not received appropriate therapy for acute prostatitis. Foreign bodies and urinary tract obstruction are other predisposing factors. In the past, *Neisseria gonorrhoeae* was a common pathogen, but most cases now are caused by the common uropathogens. Infection generally occurs by the ascending route. On occasion, *S. aureus* is the pathogen,[32] which suggests the possibility of hematogenous infection. Blastomycosis, cryptococcosis, and nocardiosis are also well-described causes of prostatic abscess. In a prospective case series of melioidosis from an endemic region, prostatic abscess caused by *Burkholderia pseudomallei* was commonly observed.[75]

Patients are usually febrile with irritative and obstructive voiding symptoms, and they may have signs of sepsis. The clinical presentation closely resembles that of acute bacterial prostatitis. The classic abscess presentation is a fluctuant area in the prostate when palpated during rectal examination. The presentation may be subtle, however. Ultrasonography, computed tomography (Fig. 110.2), or magnetic resonance imaging of the pelvis is helpful for confirming the diagnosis or in patients with equivocal clinical findings. Treatment includes draining the abscess through a perineal or a transurethral route and appropriate antimicrobial therapy for 4 to 6 weeks.[76]

EPIDIDYMITIS

Epididymitis is an inflammatory reaction of the epididymis to various infectious agents or to local trauma. There are approximately 600,000 cases of epididymitis annually in the United States, most of which occur in men between 18 and 35 years of age.[77] Acute epididymitis has been responsible for more days lost from military service than any other disease and was responsible for 20% of urologic hospital admissions in military populations.[78]

Patients with epididymitis usually complain of painful swelling of the scrotum. The onset may be acute, over 1 or 2 days, or more gradual and often is accompanied by dysuria or irritative lower urinary tract symptoms. Many patients have a urethral discharge. Specific attention should be directed toward eliciting a past history of genitourinary tract disease or sexual exposure. Some patients may have only a nonspecific finding of fever or other signs of infection. This presentation is particularly common in hospitalized patients who have undergone recent urinary tract manipulation and who may be obtunded by medication.[79]

Tender swelling, frequently accompanied by erythema and generally unilateral, may be noted primarily in the posterior aspect of the scrotum. If the patient is examined early in the course of the disease, the swelling

may be localized to one portion of the epididymis. Later, involvement of the ipsilateral testis is common, producing an epididymo-orchitis, and it may be difficult to distinguish the testicle from the epididymis within the inflammatory mass. Scrotal examination commonly reveals the presence of a hydrocele caused by the secretion of inflammatory fluid between the layers of the tunica vaginalis. Urethral discharge may be apparent on inspection or stripping of the urethra.

There are two common types of epididymitis: nonspecific bacterial epididymitis and sexually transmitted epididymitis. Epididymitis also may occur rarely after genital trauma or with disseminated infections.

Nonspecific Bacterial Epididymitis

The most common cause of epididymitis in men older than 35 years and who are at low risk for sexually transmitted infections is infection due to coliform or *Pseudomonas* species.[80,81] In most series, gram-negative aerobic rods caused more than two-thirds of bacterial epididymitis cases. Enterococci also have been reported as pathogens.[82]

Many patients who develop bacterial epididymitis have underlying urologic pathology or have a history of recent genitourinary tract manipulation. Urologic abnormalities are especially common in children who present with epididymitis.[83] The development of epididymitis after surgery or urethral catheterization may occur weeks or, rarely, months after the manipulation. Epididymitis is particularly likely in patients who undergo urinary tract surgery or instrumentation while they are bacteriuric. Acute and chronic bacterial prostatitis is another important predisposing condition for the development of bacterial epididymitis.

Bacterial epididymitis may be an important focus of organisms causing bacteremia and local morbidity in patients with indwelling transurethral catheters. Genitourinary tract complications of acute bacterial epididymitis that occur rarely include testicular infarction, scrotal abscess, pyocele, a chronic draining scrotal sinus, chronic epididymitis, and infertility.

Tuberculous epididymitis is the most common manifestation of male genital tuberculosis, with orchitis and prostatitis seen less commonly.[84] The usual symptom is a sensation of heaviness or swelling. There is characteristic scrotal swelling with beadlike enlargement of the vas deferens. Chronic draining scrotal sinuses may be a feature. Genitourinary tuberculosis may be transmitted by direct inoculation during sexual activity and is an important cause of infertility in regions of the world where tuberculosis is endemic.[85] The systemic mycoses rarely may cause epididymitis; blastomycosis is the most common pathogen and may cause a draining sinus through the scrotal wall.[70] Brucellosis is also well described as a cause of epididymitis in patients with a history of exposure.[86] Nocardia has been described as a cause of epididymitis in immunosuppressed patients.[87] Iatrogenic cases of epididymitis and orchitis may complicate bacille Calmette-Guérin therapy for transitional cell carcinoma of the bladder.[88] Rare patients develop epididymitis as a complication of collagen vascular disorders[89,90] or as a complication of amiodarone therapy.[91]

Medical management is appropriate for most patients with bacterial epididymitis. Initial empirical treatment with agents appropriate for gram-negative rods and gram-positive cocci should be initiated pending urine culture and sensitivity results. Nonspecific measures, such as bed rest, scrotal elevation, analgesics, and local ice packs, are helpful. Surgery may be necessary for the management of complications of acute epididymal infections, such as testicular infarction, abscess, or pyocele of the scrotum.[92]

Sexually Transmitted Epididymitis

Sexually transmitted epididymitis is the most common type of epididymitis in young men. *Chlamydia trachomatis* and *N. gonorrhoeae* are the major pathogens in this population.[93] Acute epididymitis caused by sexually transmitted enteric organisms, such as *E. coli,* may also occur among men who are the insertive partner during anal intercourse.[94] Chlamydiae have been identified as the most common cause of epididymitis in younger, sexually active populations. These patients formerly were considered to have idiopathic nonspecific epididymitis.[95] One study documented infections with *C. trachomatis* in 16 (47%) of 34 cases of epididymitis in patients younger than 35 years and in only 1 of 16 cases of epididymitis in patients older than 35.[95] Patients with chlamydial epididymitis frequently do not complain of urethral discharge; however, 11 of 17 patients with epididymitis caused by chlamydiae had demonstrable discharge, usually the scant watery discharge characteristic of nonspecific urethritis. The median interval from the last sexual exposure was 10 days (range, 1 to 45 days).[95] Patients may carry chlamydiae for long periods before developing overt epididymitis.

Before the availability of penicillin, it was estimated that epididymitis occurred in 10% to 30% of men with gonococcal urethritis. In more recent studies, *N. gonorrhoeae* was identified as the cause of acute epididymitis in 16% of cases in military populations and in 21% of cases in civilians younger than 35 years.[95] Many patients with gonococcal epididymitis do not have a history of urethral discharge, and a discharge may be demonstrable in only 50% of these patients.

Underlying genitourinary tract abnormalities are uncommon in patients with sexually transmitted epididymitis. Diagnosis depends on a high index of clinical suspicion, evaluation for presence of urethritis (which may be asymptomatic), and appropriate diagnostic tests, including nucleic acid amplification testing for *C. trachomatis* and for *N. gonorrhoeae*. Specific antibiotic therapy, using drugs appropriate for chlamydial and gonococcal infections, is the most important aspect of treatment. Because of emerging antibiotic resistance identified in *N. gonorrhoeae* isolates, combination therapy with intramuscular ceftriaxone plus either azithromycin or doxycycline is currently recommended.[93] For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea and enteric organisms (in men who practice insertive anal sex), intramuscular ceftriaxone and oral levofloxacin or ofloxacin is recommended.

Patients should be evaluated for other sexually transmitted infections, and treatment of sexual partners is important. In general, a complete urologic workup is not indicated for patients with uncomplicated sexually transmitted epididymitis. Rare complications of sexually transmitted epididymitis include abscess formation, testicular infarction, chronic epididymitis, and infertility. Ultrasonography, particularly color-flow Doppler ultrasonography, is useful for the differential diagnosis of complicated cases of epididymitis.[96,97]

Follow-Up

Failure of the signs and symptoms of epididymitis to subside within 3 days requires reevaluation of the diagnosis and the therapy.[93] Persistent swelling and tenderness after completion of therapy suggest the need for comprehensive evaluation. Considerations in the differential diagnosis include abscess, infarction, testicular cancer, and tuberculous or fungal epididymitis. Some patients develop chronic scrotal pain that is difficult to manage and may, on occasion, merit consideration of surgical procedures.[98]

ORCHITIS

Orchitis is inflammation of the testis, but the term has also been used to describe pain localized to the testis without objective evidence of inflammation. Isolated orchitis is significantly less common than prostatitis or epididymitis. Orchitis differs from other infections of the male accessory sex glands in two important respects: bloodborne dissemination is the major route of infection, and viruses are implicated as important pathogens.

Viral Orchitis

Viral infections, particularly mumps,[99] are associated with most cases of orchitis. Although mumps rarely causes orchitis in prepubertal boys, orchitis occurs in approximately 20% of postpubertal males with mumps. Testicular pain and swelling usually begin 4 to 6 days after the onset of parotitis but may occur without parotid involvement. Orchitis is unilateral in approximately 70% of cases. Contralateral testicular swelling may occur 1 to 9 days after involvement of the first side. The clinical course is variable and ranges from mild testicular discomfort and swelling to severe testicular pain and marked swelling accompanied by nausea, vomiting, prostration, high fever, and constitutional symptoms. Epididymitis and inflammation of the spermatic cord may be noted on physical examination. Resolution of mild cases may occur in 4 to 5 days; more severe cases usually resolve in 3 to 4 weeks. In approximately half of cases, the involved testes undergo some degree of atrophy. In

older series, sterility was reported in 25% of patients with bilateral disease. More recent studies have found, however, that mumps orchitis seldom results in infertility.[100]

Coxsackie B virus produces a disease that clinically and histologically resembles mumps orchitis.[101] Infection with lymphocytic choriomeningitis virus occasionally can result in orchitis, which develops 1 to 3 weeks after the onset of the initial fever. Orchitis is usually unilateral and painful. Most cases resolve within 2 weeks.[102]

Bacterial Orchitis

With the exception of viral diseases, acute genitourinary tract infections involving only the testis are distinctly unusual. Pyogenic bacterial orchitis usually occurs because of contiguous spread from an inflammatory process in the epididymis that causes an epididymo-orchitis. Most cases of pyogenic orchitis are caused by *E. coli, Klebsiella pneumoniae, P. aeruginosa,* staphylococci, or streptococci. On occasion, acute orchitis may be caused by other organisms as a result of hematogenous seeding. This seeding seems to be a particular risk with brucellosis in endemic areas. Rare cases of syphilitic orchitis have been described.[103]

A patient with pyogenic orchitis appears acutely ill, with high fever and marked discomfort and swelling of the involved testicle. In general, the pain is described as radiating to the inguinal canal, and it frequently is accompanied by nausea and vomiting. On examination, there is usually an acute hydrocele. The testis is swollen and exquisitely tender.

The overlying scrotal skin is generally erythematous and edematous. Complications of pyogenic bacterial orchitis include testicular infarction, abscess formation, and pyocele of the scrotum. Surgery usually is required for treatment of these conditions. Orchitis can be caused by tuberculosis and blastomycosis, usually by extension from the epididymis.[84,104] Involvement of the testicle without palpable abnormality in the adjacent epididymis rarely has been observed with these agents.

UROLOGIC MANIFESTATIONS IN MEN WITH HIV INFECTION

One autopsy study of 140 patients with HIV/AIDS found that 2 of 17 cases with systemic toxoplasmosis and 4 of 65 cases of systemic cytomegalovirus infection involved the testes.[105] Other opportunistic infections involving the male genital tract include those caused by mycobacteria, cryptococcosis, *Aspergillus fumigatus* and other mycoses, *Haemophilus parainfluenzae,* and candidiasis.[106] The testes characteristically exhibit azoospermia, marked spermatogenic arrest, germ cell degeneration, peritubular fibrosis, and Leydig cell depletion. These nonspecific findings probably reflect the severe systemic disease in these patients.

Other urologic manifestations in patients with HIV infection reflect involvement of related organ systems. Bladder dysfunction may occur in patients with HIV-associated neurologic disorders. This bladder dysfunction increases the risk of urinary tract infection, which was diagnosed in 14% to 20% of HIV-positive patients in one series.[107] HIV status was an independent risk factor for bothersome lower urinary tract symptoms in a recent study of men who have sex with men, and severe urinary symptoms were more likely to be reported in HIV-positive men with a history of AIDS.[108] In another report, bacterial prostatitis was diagnosed in 17 (8%) of 209 men hospitalized for treatment of HIV-related infections.[109] The prevalence of bacterial prostatitis was observed to increase from 3% in HIV-asymptomatic patients to 14% in patients with AIDS.

SEMEN AS A VECTOR FOR HIV INFECTION

The relative contributions of behavioral and clinical risk factors to transmission of HIV are incompletely understood, but sexual activity alone provides a limited explanation. Expressing risk as a function of frequency and types of sexual contacts has not yielded straightforward patterns; this probably reflects biologic factors that determine infectiousness and the vulnerable partner's susceptibility. Stage of disease and other host factors; male circumcision; genital and plasma HIV viral load; viral characteristics, such as tropism and syncytium-inducing capability; and antiretroviral treatment have been linked to greater and lesser degrees of infectivity.[110]

Studies demonstrate that other sexually transmitted infections increase the risk of HIV transmission and acquisition[111] and suggest that their treatment may reduce the sexual transmission of HIV.[112,113] Sexually transmitted infections are believed to increase susceptibility to HIV infection by recruiting target cells and disrupting epithelial barriers. In addition, genital ulcer diseases and urethritis (gonococcal and nongonococcal) increase the HIV viral load in semen.[114] In contrast, sexually transmitted infection treatment reduces HIV shedding.

Epidemiologic studies have suggested that direct contact with semen is the most important route for HIV sexual transmission. HIV type 1 first was isolated by cocultivation of seminal cells and donor lymphocytes.[115] Shedding of HIV in semen was associated with no significant changes in semen parameters that assessed fertility in one study of 50 semen specimens from asymptomatic or minimally symptomatic HIV-positive men.[116] In contrast, three men with AIDS all had pyospermia and grossly abnormal sperm. Abnormalities in the semen of men with AIDS likely reflect severity of disease but do not correlate with seminal shedding of HIV.

Semen is composed of cell-free seminal plasma and seminal cells (mature spermatozoa, immature sperm forms, leukocytes, and epithelial cells). Two approaches have been used to determine the likely sources of HIV within the semen. The first approach is to fractionate and analyze ejaculated semen specimens.[117] These studies have suggested that most viable (i.e., culturable) HIV in semen is cell associated, particularly with T lymphocytes and macrophages but not with motile spermatozoa. The second approach is anatomic, based on the observations that vasectomy causes dramatic reductions in seminal cells and eliminates secretions from proximal sites in the male reproductive tract. HIV RNA was assayed in seminal plasma and HIV DNA in seminal cells from 46 asymptomatic seropositive men before and after vasectomy.[118] Vasectomy produced no significant changes in levels of HIV RNA or DNA, supporting the conclusion that most seminal HIV is not associated with germinal cells but arises from distal sites in the male reproductive tract.[119]

Several lines of evidence support the idea that the male genital tract may be distinct from the systemic immune compartment.[120] Qualitative and quantitative virologic measurements from blood and genital compartments have suggested lack of association between culturability of virus in semen and viral RNA level in blood, discordant distribution of phenotypes, discordant viral RNA levels, a weak correlation between viral RNA level in semen and $CD4^+$ lymphocyte count in blood, differences in the biologic variability of viral RNA levels, and differences in the viral load response to antiretroviral therapy.[120] Phylogenetic studies have also supported the concept of compartmentalization.[121] Some, but not all,[122] studies have suggested a weak correlation between HIV RNA levels in the blood plasma and HIV RNA levels in the seminal plasma. However, neither HIV RNA blood level nor the $CD4^+$ lymphocyte count reliably predicts shedding of culturable virus or detection of viral RNA in the semen.[120] A study demonstrating that higher seminal HIV RNA levels were associated with a greater risk of heterosexual HIV transmission, independent of plasma HIV concentrations, suggests that HIV RNA in semen could be used as a marker of HIV sexual transmission risk.[123] Factors that may influence the HIV viral load in seminal fluid include systemic illness, antiretroviral therapy, urethritis, male genital tract inflammation, reactivation of genital herpesvirus infection, and seminal shedding of cytomegalovirus or other viruses. If the male reproductive tract is a distinct immunologic compartment, factors determining the infectiousness of semen may differ substantially from the factors determining HIV levels in blood, lymphatic tissue, or the central nervous system.

Whether detectable virus in the genital fluid when plasma virus is undetectable is of importance in transmission risk in serodiscordant couples is unclear based on recent clinical trials data. Three landmark studies—the HPTN 052, PARTNER, and Opposites Attract studies—have provided the strongest evidence to date that effective antiretroviral therapy prevents sexual transmission of HIV.[124–127] Across all three studies, no linked HIV transmissions were observed between mixed-HIV-status partners when the partner with HIV had virologic suppression (defined in these studies as having a plasma HIV RNA level less than either 200 or 400 copies/mL). Based on these research findings, the US Centers for Disease Control and Prevention (CDC) issued a prevention message

that people with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex.[128]

SEMEN AS A VECTOR FOR ZIKA VIRUS INFECTION

Zika virus (ZIKV) is a flavivirus that has been linked to adverse birth outcomes and to the Guillain-Barré syndrome. Although ZIKV is primarily transmitted to humans by the bite of an infected *Aedes* species mosquito, it can also be transmitted through unprotected sex with an infected partner, including asymptomatic individuals. Numerous reports describe the detection of ZIKV RNA in semen, but finding ZIKV RNA in semen might not indicate the presence of infectious virus at the time of sampling, or correlate with the potential for sexual transmission of ZIKV. The largest published prospective cohort study to date included 184 symptomatic men with documented ZIKV infection from whom semen samples were obtained at 2-week intervals for 6 months following onset of illness.[129] Detectable ZIKV RNA was found in 61% of participants who submitted samples within 30 days, with the proportion decreasing to 7% or less in those who submitted samples more than 90 days after illness onset. ZIKV RNA persisted for 9 months is some men, which was consistent with previous reports. Infectious ZIKV was isolated in 3 of 78 samples with detectable RNA that were tested by culture, and all were obtained within 30 days of illness onset. Among the currently available reports of sexual transmission of ZIKV, the longest period from symptom onset in the index case to potential sexual transmission to a partner was between 32 and 41 days.[130] Current CDC guidelines for men with possible ZIKV exposure who are planning to conceive with their partner recommend waiting for at least 3 months after symptom onset (if symptomatic) or their last possible ZIKV exposure (if asymptomatic) before engaging in unprotected sex. The CDC also recommends that for couples who are not trying to conceive, men can consider using condoms or abstaining from sex for at least 3 months after symptom onset (if symptomatic) or their last possible ZIKV exposure (if asymptomatic) to minimize their risk for sexual transmission of ZIKV.[130]

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The complete reference list is available online at Expert Consult.

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M Eye Infections

111 Introduction to Eye Infections

Marlene L. Durand

Vision loss affects daily life in so many ways that most people value their sight more than any other special sense. Eye infections that result in permanent vision loss can be devastating, and many eye infections rapidly threaten sight if not promptly diagnosed and treated. Infectious disease physicians appreciate how important their help may be to ophthalmologists but may find it difficult to interpret the ophthalmologist's notes and specialized terminology. This brief review of eye anatomy and of the terminology commonly used by ophthalmologists may be helpful to the non-ophthalmologist caring for patients with eye infections.

ANATOMY

Several points about eye anatomy are worth considering.

1. From an embryologic perspective, the globe of the eye may be thought of as having three "coats" (cornea and sclera; uvea; retina) and two humors (aqueous, vitreous) (Fig. 111.1). The cornea and sclera form a protective outer coat, with the cornea as a clear window. The uvea is the highly vascularized and pigmented middle coat and is composed of the iris, ciliary body, and choroid. The retina, embryologically, is an outpouching of the brain.
2. The eye is divided into anterior and posterior *segments* by the lens (the dividing line is just behind the lens). Aqueous humor (0.25 mL) fills the anterior segment, and vitreous (4 mL) fills the posterior segment.
3. Aqueous humor is a liquid that is continuously produced and reabsorbed, with a turnover time of approximately 100 minutes. In contrast, the vitreous humor is a gel-like substance that forms in utero and is never regenerated. The rapid turnover of aqueous but persistence of vitreous is one reason why a break in the posterior lens capsule during cataract surgery greatly increases the risk of postcataract endophthalmitis. The aqueous is commonly contaminated by ocular surface flora during eye surgery, but these bacteria are usually cleared unless they reach the vitreous (see Chapter 114).
4. There is a blood-eye barrier similar in many respects to the blood-brain barrier. Many antibiotics that penetrate the blood-brain barrier also penetrate the blood-eye barrier and therefore may be good choices for treating intraocular infections.

TYPES OF EYE INFECTIONS

Patients with most types of eye infections have no systemic evidence of infection and usually feel well, aside from their eye. The exceptions are patients with endogenous endophthalmitis, some types of uveitis, and orbital infections. However, even patients with these types of eye infections may be afebrile and have a normal white blood cell count.

Conjunctivitis

Conjunctivitis is characterized by eye irritation or discomfort but not significant pain unless there is also involvement of the cornea. The latter is then termed *keratoconjunctivitis* and may lead to corneal scarring (see Chapters 112 and 113).

Keratitis

Keratitis refers to infection of the cornea (see Chapter 113). The cornea is only 0.5 mm thick in the center and has a five- to seven-cell–thick epithelium overlying the stroma and endothelium. Keratitis may occur in the epithelium only (e.g., dendritic keratitis in an initial episode of herpes simplex keratitis), the stroma or interstitium (e.g., interstitial keratitis of syphilis), or both as an infiltrate or ulceration (e.g., *Pseudomonas* keratitis). In cases of large corneal infiltrates or ulcerations, the keratitis may be appreciated even with a flashlight examination at the bedside.

Along with the overlying tear film, the cornea provides 65% to 75% of the refractive power of the eye, so keratitis usually causes decreased vision. The cornea has no blood vessels but many nerve endings, so keratitis is typically painful. Patients with decreased corneal sensation, such as from repeated attacks of herpetic keratitis, may not appreciate that they have a corneal infection until it is advanced.

Endophthalmitis

Endophthalmitis refers to bacterial or fungal infection inside the eye involving the vitreous, the aqueous, or both (see Chapter 114). Infection may be introduced exogenously (i.e., from the outside in), such as from eye surgery or eye trauma, or endogenously, from bacteremia or fungemic seeding of the eye. Of note, endophthalmitis does not serve as a *source* for bacteremia or fungemia except in rare cases of panophthalmitis (where there is both endophthalmitis and orbital cellulitis).

Uveitis

Uveitis refers to inflammation of the uvea (iris, ciliary body, choroid) or retina (see Chapter 115). Most cases are idiopathic or related to a rheumatologic condition, and the frequency of infectious etiologies varies by the type of uveitis. Uveitis is categorized by the location of maximal inflammation and thereby divided into four types: anterior (iritis, iridocyclitis); intermediate (pars planitis); posterior (retinitis, chorioretinitis, choroiditis); or panuveitis. It is important to understand the type of uveitis, because the differential diagnosis and the likelihood of an infectious etiology vary according to the anatomic category.

Periocular Infections

Periocular infections are those involving the soft tissues surrounding the globe of the eye (see Chapter 116). The term *periocular* is not precise and encompasses both *preseptal* and *orbital.* It is important to distinguish preseptal from orbital infections. Preseptal infections, also sometimes called "periorbital" infections, involve the superficial (preseptal) part of the lids and do not threaten vision. Orbital infections (orbital cellulitis, subperiosteal abscess, orbital abscess) are much more serious and are often vision threatening. The two conditions may be distinguished at physical examination; orbital infections cause one or more "orbital signs" (decreased vision, limitation in extraocular movement, proptosis), whereas preseptal infections do not. Of note, the proptosis may not be obvious at gross examination and may be detected only with use of a Hertel exophthalmometer. A difference between the eyes of 2 mm or more is significant.

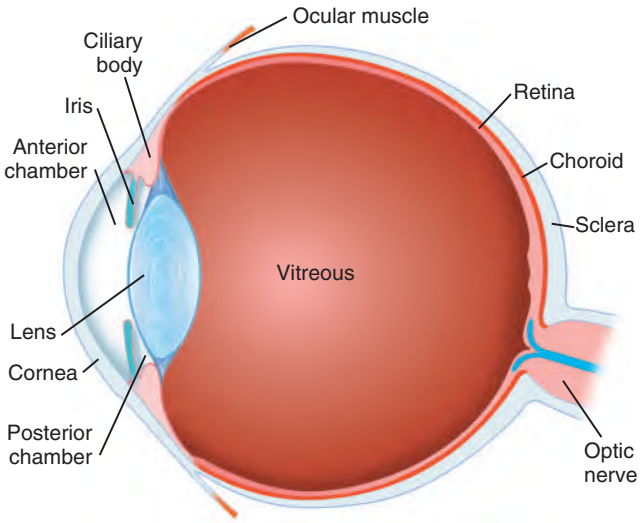

FIG. 111.1 Diagram of the eye.

UNDERSTANDING THE OPHTHALMOLOGIST'S NOTE

The ophthalmologist's examination starts with visual acuity and intraocular pressure (IOP) measurements and then proceeds in sequence from the surface of the eye to the fundus. The ophthalmologist uses a slit lamp and indirect ophthalmoscope for a complete examination. The direct ophthalmoscope, used by most non-ophthalmologists, does not show most corneal abnormalities or the degree of intraocular inflammation or provide a full view of the fundus. Perhaps as a consequence, many serious eye infections are initially misdiagnosed as conjunctivitis by the non-ophthalmologist. Symptoms that distinguish more serious eye infections from conjunctivitis include decrease in baseline vision and eye pain. Patients with these symptoms should be referred to an ophthalmologist for an urgent examination.

Visual Acuity and Measuring Low Vision

The ophthalmologist's note usually starts with a measurement of visual acuity. This is measured both "with correction" and "without correction," meaning correction of refractive error (e.g., through use of glasses). A "pinhole" visual acuity is measured by having the patient look through a card with a pinhole in it. This mimics optimal refraction and distinguishes visual loss due to uncorrected refractive error from more serious etiologies.

Patients with low vision are particularly affected by lighting conditions, and the non-ophthalmologist should keep this in mind. Patients being examined at the bedside in a dimly lit hospital room may have better vision when examined under good lighting.

The best visual acuity the patient can achieve with each eye is always recorded. Patients with serious eye infections may have worse vision than can be measured with the Snellen eye chart; the "big E" at the top of the chart is 20/400 vision. If the patient has very low vision, it is recorded as one of the following, in descending order: "count fingers" (CF), "hand motion" (HM), or "light perception" (LP). For count fingers vision, the distance of the examiner's fingers is recorded, so "CF at 3 feet" is recorded and represents better vision than "CF at 1 foot." If the patient cannot detect a bright light shining directly in his or her eye, he or she has "no light perception" (NLP) vision, or complete blindness in that eye. Visual recovery from NLP is extremely unlikely in an infected eye unless the NLP recording is transient. Any vision better than NLP is worth saving, and an aggressive approach to eye infections is important; patients value even LP vision. In addition, there are many factors that affect vision in the setting of an acute eye infection, and some of these are reversible. The patient's vision 3 months after an acute bacterial endophthalmitis, for example, is usually much better than it is 3 days after presentation.

TABLE 111.1 Common Abbreviations

ABBREVIATION	MEANING
OD	Right eye
OS	Left eye
OU	Both eyes
V_A	Visual acuity. By convention, the right eye vision is given above the left, so the following symbol means that the right eye vision is 20/30 and left eye vision is 20/50: V_A 20/30 / 20/50
BCVA	Best corrected visual acuity (meaning with refractive error corrected, e.g., patient wearing glasses)
PH	Pinhole, used to mimic glasses in order to quickly correct for refractive error and give a measurement close to the best corrected visual acuity
CF	Count fingers vision (best vision is ability to count fingers; often given with distance of examiner's fingers from face)
CF @ 3 feet	Patient can count fingers when fingers are 3 feet away (better, e.g., than CF @ 1 foot)
HM	Hand motion (best vision is ability to detect when the examiner's hand is moving)
LP	Light perception (best vision is ability to tell when a light source, such as a flashlight, is turned on or off)
NLP	No light perception
T	Tonometry measurement of intraocular pressure; as with visual acuity, the right eye pressure is listed above the left eye pressure
IOP	Intraocular pressure—normal is 10–20 mm Hg
AC	Anterior chamber
PC	Posterior chamber (note that this is part of *anterior segment* of the eye)
IOL	Intraocular lens. This artificial lens is placed in the eye during cataract surgery to help with refraction; it is nearly always placed in the posterior chamber (the part of the anterior segment between iris and lens)
PCIOL	Posterior chamber intraocular lens (the usual location of the IOL)
K	Cornea

Intraocular Pressure

The IOP is usually measured with a tonometer, so a symbol of "T" is often listed in the ophthalmologist's note. Normal IOP is 10 to 20 mm of mercury, and both very low and very high pressures are dangerous to the eye. Very low pressure may occur in a keratitis case, for example, if the corneal infection has led to a corneal perforation and aqueous humor leak. High IOP often occurs in cases of acute endophthalmitis or infectious uveitis in which there is marked inflammation. High IOP must be treated to prevent glaucomatous damage to the eye.

Ophthalmology Examination

The ophthalmologist records the eye examination findings from front to back, starting with the lids and adnexae and ending with the funduscopic examination. Common abbreviations used are listed in Table 111.1. To illustrate the interpretation of an ophthalmology note, the following are examples of eye infection cases referred for infectious diseases consultation. Interpretation of each line of the note is listed in italics.

Case Example 1

A 65-year-old woman with multiple medical problems presented with 5 weeks of painless decrease in vision in her right eye. This had been

her better eye, with baseline visual acuity of 20/40. The onset of symptoms was 2.5 months after she had been hospitalized with pneumonia and treated with intravenous antibiotics for 10 days via a peripherally inserted central catheter.

Ophthalmologist's Examination

Exam OD (OD = right eye):
V_A sc LP; PH NI
*(**V**isual **A**cuity without correction is **L**ight **P**erception only; **P**in**h**ole examination shows **N**o **I**mprovement)*
IOP 15 *(**I**ntra**o**cular **P**ressure is 15 mm Hg)*
lids—normal
conj—mild injection *(conj = conjunctiva)*
K—mild edema *(K = cornea)*
AC—3+ cells, no hypopyon *(**A**nterior **C**hamber has 3+ white blood cells, on a scale of 0 to 4+ with 0 being normal. There is no hypopyon, meaning no layer of white blood cells in the anterior chamber. A hypopyon is illustrated in Chapter 114.)*
iris—WNL *(within normal limits)*
lens—PC IOL *(The native lens has been replaced by an artificial **i**ntra**o**cular **l**ens, placed in the **p**osterior **c**hamber, which is the usual location.)*
fundus: vitreous 4+ cells, retina hazy view—? retinal infiltrate supratemporally *(Vitreous has 4+ white blood cells, on a 0 to 4+ scale with 0 being normal. This eye therefore has marked vitritis and this produces a hazy view of the fundus, so details such as a retinal infiltrate are difficult to see. The funduscopic photograph of this case is shown in Fig. 111.2.)*

Discussion

The ophthalmologist's interpretation in this case was panuveitis. The differential diagnosis of panuveitis is discussed in Chapter 115. The patient's diagnosis was endogenous *Candida* endophthalmitis, presumably from transient candidemia 4 months earlier while she had an indwelling central venous catheter.

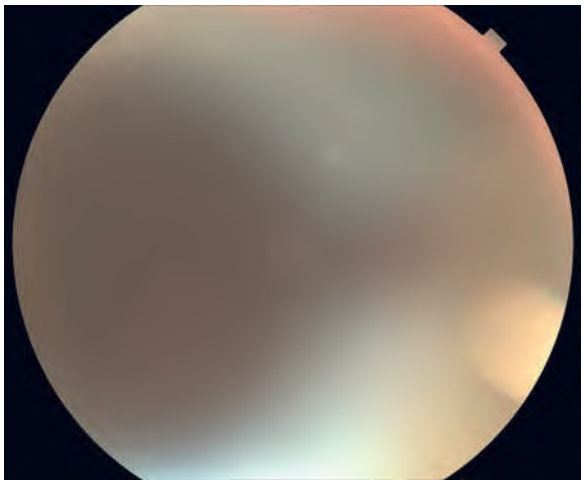

FIG. 111.2 Funduscopic photograph in a case of endogenous *Candida* endophthalmitis.

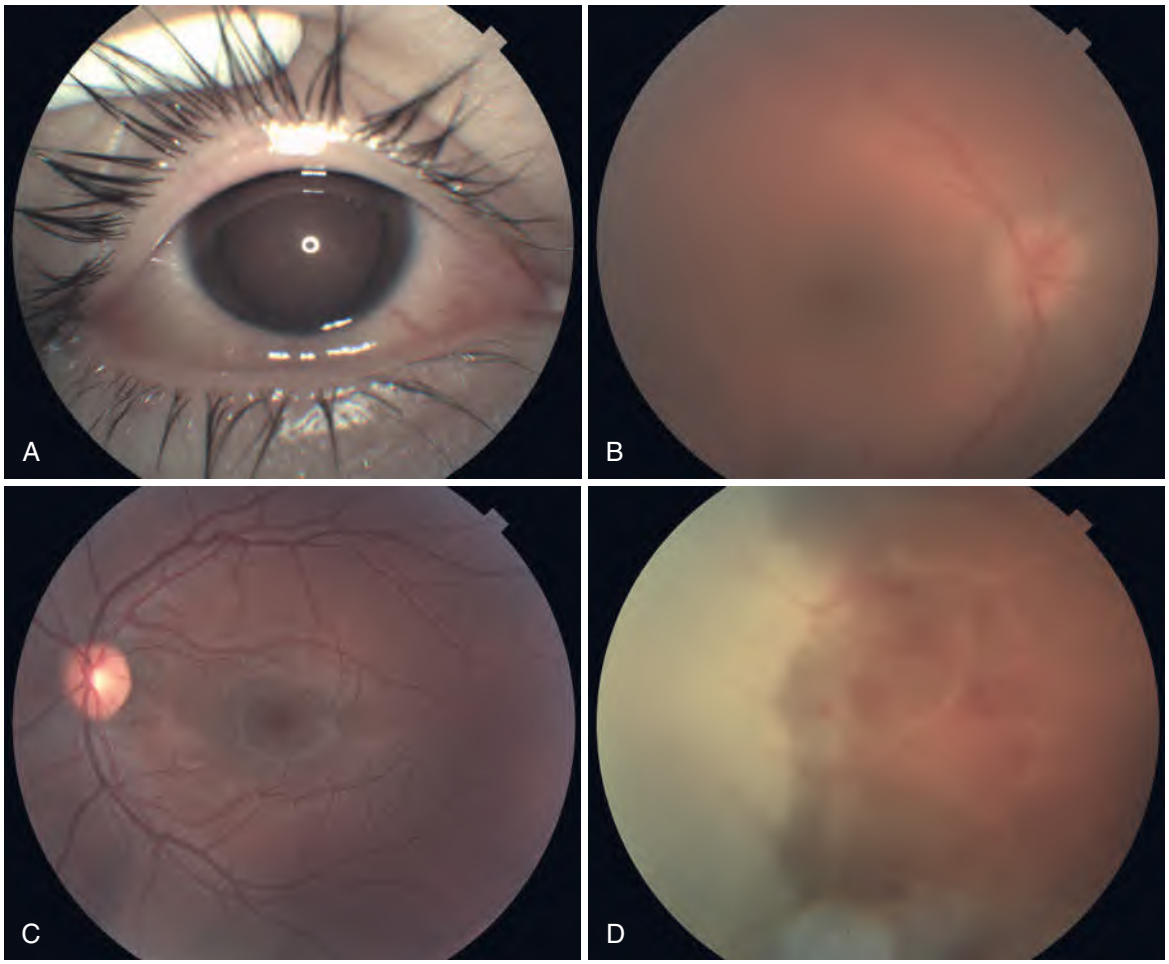

FIG. 111.3 A 19-year-old previously healthy patient with acute retinal necrosis in his right eye. The cause was herpes simplex. (A) External view. (B) Limited funduscopic view of affected eye. (C) Funduscopic view of the patient's other (normal) eye. (D) View of periphery of retina, showing the peripheral necrotizing retinitis and vasculitis (whitening and hemorrhage).

Case Example 2

A 19-year-old otherwise healthy man presented to his college infirmary with a 1-day history of right eye redness but no drainage. He had no history of prior eye problems and did not wear contact lenses. He was initially misdiagnosed with conjunctivitis and prescribed a topical antibiotic. Over the next 3 days, he developed blurring in his peripheral vision and eye pain. He was referred to an ophthalmologist.

Ophthalmologist's Examination

Exam OD *(right eye)*:
V_A—20/70
T—15 *(normal intraocular pressure)*
Lids—normal
Conjunctiva = normal
K = clear *(cornea clear)*
AC = 3+ cells *(3+ white blood cells in the anterior chamber)*
Lens = clear
Fundus: vitreous 3+ cells *(white blood cells)*, blurred disk margins, peripheral retinal whitening with vasculitis

Discussion

The external view of the right eye (Fig. 111.3A) shows injection but no discharge. The patient's eye pain and decreased vision exclude the diagnosis of conjunctivitis. The view of the fundus (Fig. 111.3B) is hazy owing to the intraocular inflammation (3+ white blood cells in aqueous and vitreous, as noted in the ophthalmologist's examination). This is in contrast with the clear view of the fundus in the patient's left (normal) eye (Fig. 111.3C). Examination of the affected eye with the indirect ophthalmoscope shows the peripheral necrotizing retinitis: areas of whitening due to retinal necrosis, and hemorrhage due to vasculitis, as noted in the ophthalmologist's note. The ophthalmologist correctly diagnosed acute retinal necrosis, a vision-threatening viral retinitis usually due to either herpes simplex or herpes zoster and discussed further in Chapter 115. This infection often occurs in otherwise healthy patients, as in this case, and is due to reactivation of latent virus.

OPHTHALMIC GLOSSARY OF INTEREST TO THE INFECTIOUS DISEASES PRACTITIONER

Aphakic, pseudophakic: An aphakic eye has no lens. A pseudophakic eye has a natural lens replaced with a prosthetic lens.

Fluorescein staining of the cornea: Useful in visualizing corneal ulcerations, such as herpetic keratitis.

Homonymous hemianopia: Loss of the left or right visual field, the same in both eyes.

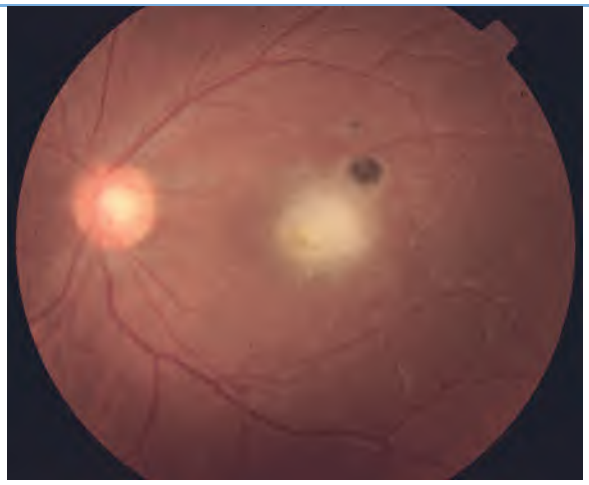

FIG. 111.4 Funduscopic photograph of a patient with reactivation ocular toxoplasmosis. New active lesion (creamy yellow) adjacent to a black "scar" from a prior episode. The new lesion threatens the macula.

LASIK (laser-assisted in situ keratomileusis): Laser eye surgery to reshape the cornea in order to correct refractive error.

OCT (optical coherence tomography): Noninvasive method to visualize the retina and subretinal tissue in cross section. Usually used for macular degeneration or diabetic retinopathy but can be used for evaluation of papilledema, subretinal fluid, and subretinal masses.

Pars plana vitrectomy: Surgical removal of a portion of the vitreous humor for diagnostic and/or therapeutic reasons (e.g., diagnosis and treatment of endophthalmitis; see Fig. 114.3).

Scotoma: An area in the visual field with altered or no vision, surrounded by normal vision.

CONCLUSION

Ophthalmologists treat most eye infections without consulting an infectious diseases specialist. A patient presenting to an ophthalmologist with decreased vision and the funduscopic findings shown in Fig. 111.4, for example, would not usually be referred to an infectious diseases physician. This case would be readily diagnosed by the retina specialist as ocular toxoplasmosis because the appearance of the fundus is classic for that disease. However, ophthalmologists may refer patients in whom a diagnosis is in question or in whom the usual treatment for a presumed diagnosis is failing. In these cases, collaboration between the ophthalmologist and the infectious diseases specialist may prove invaluable.

112 Microbial Conjunctivitis

Nalin M. Kumar, Scott D. Barnes, Deborah Pavan-Langston, and Dimitri T. Azar

SHORT VIEW SUMMARY

Definition
- Microbial conjunctivitis involves inflammation of the thin lining of the inner eyelid and front of the eyeball caused by bacteria, viruses, fungi, or parasites.

Epidemiology
- Conjunctivitis affects male and female patients of all ages.
- Viruses are the most common cause of infectious conjunctivitis, with bacteria being the second most frequent agent.
- Bacterial conjunctivitis is more prevalent in children; viral conjunctivitis is more prevalent in adults.
- Risk factors include contact lens wear, contaminated ocular medications, exposure to an infected person, vaginal versus cesarean delivery, and visits to camps and swimming pools.

Microbiology
- Nonherpetic viral conjunctivitis and bacterial conjunctivitis are the most common causes of infectious conjunctivitis.
- Common causes of bacterial conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus* spp., *Moraxella, Corynebacterium diphtheriae, Neisseria* spp., and enteric gram-negative rods.
- The most common cause of viral conjunctivitis is infection with adenovirus, but other viral causes include herpes simplex virus (HSV), enterovirus, and varicella-zoster virus.
- Neonatal conjunctivitis is commonly due to transmission from the mother during childbirth of sexually transmitted bacteria including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Diagnosis
- Symptoms of conjunctivitis include itching, increased ocular secretions, swelling of the conjunctiva or eyelids or both, pink color in the white of the eyes, and light sensitivity.
- Clinical presentation of acute bacterial conjunctivitis includes rapid onset of unilateral lid edema, adherence of the eyelids on waking, conjunctival injection, mucopurulent discharge, and involvement of the second eye within 1 to 2 days. Itching is uncommon. In contrast to viral and chlamydial conjunctivitis, there is no preauricular lymphadenopathy.
- Clinical presentation of viral conjunctivitis is acute, unilateral conjunctivitis with involvement of the second eye occurring often within 1 week. It is associated with a watery to mucous discharge and enlargement of preauricular lymph nodes.
- Routine laboratory evaluation is not usually required except in infants in the first month of life, in whom cultures and smears for bacterial, chlamydial, and herpetic causes need to be performed.
- If bacterial conjunctivitis is suspected, conjunctival scraping for identification of bacterial species by further analysis is recommended for guidance of appropriate antibiotic therapy.
- Viral conjunctivitis can often be diagnosed from signs (e.g., common cold), symptoms (e.g., watery, rather than mucous, discharge), and patient history (e.g., such as employment as a veterinarian or poultry worker). Laboratory tests are not usually necessary.

Therapy
- Use of topical antibiotics is recommended for contact lens wearers, patients with suspected cases of chlamydial and gonococcal conjunctivitis, patients with mucopurulent discharge and eye pain, and patients with preexisting ocular surface disease.
- Acute bacterial conjunctivitis is treated with a broad-spectrum topical agent such as sulfacetamide, trimethoprim-polymyxin B, or a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) usually administered as eyedrops every 3 hours when awake for 7 to 10 days. Topical azithromycin has been shown to be effective in treating bacterial conjunctivitis with a 3-day course.
- Viral conjunctivitis spontaneously resolves within days to weeks, usually without adverse sequelae to the conjunctiva, but associated keratitis may have long-term sequelae. HSV conjunctivitis in newborns should be treated with intravenous acyclovir.
- Use of topical antibiotics in viral conjunctivitis should be avoided, as they have no role and may have adverse treatment effects.
- Use of rapid antigen tests to diagnose suspected viral conjunctivitis is recommended before treatment with antibiotics.
- Adult inclusion conjunctivitis involves systemic treatment for 3 weeks with tetracycline, doxycycline, or erythromycin, with the caution to avoid tetracycline in children younger than age 8 and in pregnant or lactating women. The use of oral azithromycin has also been found to be effective.
- For hyperacute bacterial conjunctivitis, the prevalence of penicillin-resistant organisms has made ceftriaxone the treatment of choice.
- For neonatal chlamydial conjunctivitis, if erythromycin or tetracycline ointment is applied to the conjunctival surface within 1 hour after delivery, the chance of developing chlamydial conjunctivitis is reportedly almost zero. Two weeks of oral erythromycin therapy is given to a newborn with laboratory-proven chlamydial conjunctivitis; a second course may be given if adequate resolution is not achieved with the initial treatment.
- Spread of conjunctivitis is limited by following good hygiene steps including washing hands often; washing any discharge from around the eyes multiple times during the day; and using fresh washcloths, cotton balls, or tissues each time.

CONJUNCTIVITIS

Conjunctivitis affects people of all ages and is seen in all geographic locations; it is the most common inflammation of the eye and ocular adnexa.[1,2] Conjunctivitis can be divided into infectious and noninfectious causes. The most common cause of the latter is allergy. The economic impact for prevention, diagnosis, and treatment of microbial conjunctivitis is immense.[3] The various forms of conjunctivitis caused by viruses, chlamydiae, bacteria, parasites, fungi, and antigens tend to share a number of signs and symptoms, but there are some clinical differences that suggest the appropriate identification and treatment. Conjunctivitis can be either primary or secondary to systemic diseases such as chlamydia. The patient's history and the season of the year often suggest a potential diagnosis, which may then be confirmed through clinical examination and possibly laboratory evaluation. Different agents cause acute versus chronic conjunctivitis. Onset within 4 to 6 weeks before presentation is classified as acute disease. In this chapter we describe

the anatomy and physiology of the conjunctiva and the clinical presentation and laboratory testing of microbial conjunctivitis. We discuss viral conjunctivitis, bacterial conjunctivitis, and neonatal conjunctivitis, and we end with descriptions of fungal and parasitic conjunctivitis.

ANATOMY AND PHYSIOLOGY

The inner surface of the eyelid is covered by a mucous membrane called the *conjunctiva*. This membrane lining the lids (palpebral conjunctiva) is reflected on itself, forming an inferior and superior cul-de-sac, or fornix, as it then covers the surface of the globe (bulbar conjunctiva) and extends to the edge of the cornea (limbus). These fornices form a physical barrier that prevents a foreign body (e.g., contact lens) from getting into the orbital space. In addition to connecting the lids to the globe, the conjunctiva produces mucus as part of the tear film. The conjunctiva and tear film provide protection of the ocular surface from pathogens accomplished via mechanical means and via the resident immune tissue.

The conjunctiva is made up of a superficial epithelial layer overlying the substantia propria. The conjunctival epithelium possesses goblet cells, unique among stratified, nonkeratinized epithelia. These goblet cells contribute to the production of mucins in the tear film. Corneal stem cells are known to exist at the limbus and peripheral cornea. A similar search for conjunctival stem cells has produced interesting results. Conjunctival cells with stemlike activity have been identified in rabbits, and subdermal injection of clonal cultures of conjunctival epithelium in nude mice has produced cysts with goblet cells and stratified epithelium suggesting pluripotency that seems to give rise to both cell types.[4,5] The connective tissue of the substantia propria is loose and highly vascularized, properties that allow for the dramatic clinical appearances of significant edema and injection. Abundant numbers of lymphocytes, mast cells, plasma cells, and neutrophils are found throughout the connective tissue.[6] This lymphoid tissue does not form actual lymph nodes; however, its abundance, combined with the phagocytic properties of the conjunctival epithelium, demonstrates the nature of this tissue in dealing with infectious organisms.[7]

CLINICAL PRESENTATION

History and Physical Examination

Particular attention should be paid to the time course of the condition, any inciting events, prior and current medication use, and the patient's own report of the associated symptoms. The physical examination focuses on the appearance of the periorbital skin and other mucous membranes (e.g., nasal, oral); unilaterality/bilaterality; the appearance of the conjunctiva; the associated discharge; visual acuity; and any specific facial, lid, and corneal involvement. A clinical approach that describes a flow chart for diagnosis of suspected acute conjunctivitis has been described and may be useful for initial evaluation of the patient.[8]

Eye Pain

In contrast to keratitis, ocular pain is not common with most forms of conjunctivitis. There is usually some degree of irritation, most commonly described as a foreign-body sensation. Although uncommon in most forms of conjunctivitis, the presence of ulcerated lesions in the eyelid and conjunctiva in herpetic, smallpox, and vaccinia conjunctivitis may be quite painful. If the conjunctival process secondarily affects the cornea, eye pain may also become more prominent. Therefore the presence of significant eye pain should prompt a more thorough search for lid/corneal involvement or intraocular inflammation.

Itching

Almost all patients with conjunctivitis complain of variable ocular burning and itching. However, severe itching tends to be a hallmark of the allergic and toxic causes of conjunctivitis. In addition to the resident lymphoid tissue, the conjunctiva has plentiful immunoglobulin E and mast cells. Degranulation of mast cells and histamine released in response to an inciting antigen are responsible for the significant itching.

More recent studies have focused on whether itching can be regarded as a top clinical sign and symptom for conjunctivitis. Using a logistic regression model, Rietveld and colleagues[9] reported itching as one of the three indicators that provided optimal discrimination between patients with and without a positive culture. They reported that infectious conjunctivitis history and itch both made the probability of current bacterial involvement less likely. They also noted that mattering and eyelid adherence in the morning was a stronger predictor for bacterial conjunctivitis. This information has been incorporated into the practice guidelines of the Dutch College of General Practitioners.[10]

Visual Acuity

Visual acuity is usually normal or mildly decreased with conjunctivitis. Unless the cornea has become secondarily involved, vision is preserved. The ocular irritation and discharge may affect the ability to read an eye chart; a topical anesthetic agent and surface irrigation may improve the office examination of vision. A reduction in vision should prompt a search for an associated cause other than the conjunctivitis.

Conjunctival Hyperemia

The rich network of subepithelial vessels that runs throughout the conjunctiva becomes markedly dilated and congested. Against the background of the relatively avascular sclera, this hyperemia appears quite impressive. On closer examination, the hyperemia appears greater near the conjunctival periphery than in the limbal region (near the corneal border). Saccular aneurysms, petechiae, and subconjunctival or intraconjunctival hemorrhages may be present.

Periocular and Periorbital Skin

Some cases of conjunctivitis have associated skin changes. Skin lesions typical in poxviruses, immune-mediated diseases (Stevens-Johnson syndrome), and herpetic conditions are usually not difficult to recognize; however, a close examination may help identify causes that produce less obvious skin findings. Subtle vesicular changes on the lid margin may be the only sign of an otherwise unimpressive herpetic conjunctivitis. Numerous lesions of molluscum contagiosum provide an easy diagnosis, but small, isolated lesions may be missed if they are buried near the eyelid margin or obscured by the eyelashes. Ocular rosacea is quite common and usually bilateral. Caution must be used when diagnosing rosacea in unilateral cases because sebaceous gland carcinoma can manifest in such a fashion. Allergic conjunctivitis incited by antigens such as cosmetics, soaps, lotions, and some medications often has a typical periocular dermal manifestation.

Sweet syndrome (acute febrile neutrophilic dermatosis) is commonly associated with conjunctivitis.[9] The ocular manifestations of Sweet syndrome include periorbital and orbital inflammation, dacryoadenitis, conjunctivitis, episcleritis, scleritis, limbal nodules, peripheral ulcerative keratitis, iritis, glaucoma, and choroiditis. The ocular inflammation appears concurrently with skin lesions. In addition, the syndrome can manifest with optic nerve involvement.[11] Treatment of the ocular complications of Sweet syndrome includes systemic administration of corticosteroid or cyclosporine.[12]

Discharge

Ocular secretion is almost universal in conjunctivitis. Excessive tearing results from either increased lacrimation or impaired lacrimal outflow. Increased mucin production, especially relative to the aqueous component of the tear film, is a common finding. Exudate from the conjunctival surface contains varying proportions of protein and cellular debris. A serous exudate is mainly proteinaceous; a purulent exudate is more cellular (e.g., leukocytes, fibrin). The combination of proteins, fibrin, mucin, and sloughed epithelial cells can be copious depending on the cause of the inflammation. Significant matting and "sticking together" of the eyelids and eyelashes are common.

Conjunctival Edema (Chemosis) and Conjunctivochalasis

The loosely adherent subepithelial connective tissue allows the conjunctiva an impressive degree of edema. Hemodynamic changes and altered vascular integrity allow transudation through fenestrated capillaries, resulting in chemosis. This edema can be so prominent that the conjunctiva appears to be "bulging" out from between the eyelids, and it may cause exposure of the ocular surface if the eyelids cannot adequately close. Depending on the inciting agent, the chemosis may become

hemorrhagic. Acute chemosis is often self-limited, but chronic chemosis can lead to conjunctivochalasis, or laxity of the conjunctiva, with resultant redundancy sometimes draping over the lower lid margin.

Conjunctival Papillae

The palpebral conjunctiva contains connective tissue septa that provide anchorage for the tarsus (dense connective tissue providing strength to eyelids). Conjunctival inflammation may result in dilated subepithelial blood vessels that become surrounded by an infiltrate of mixed inflammatory cells (e.g., neutrophils, lymphocytes). This edema produces elevated mounds of conjunctival epithelium, with the septa restricting diffusion beyond the fibrovascular core. The mounds, or papillae, have a central red dot corresponding to the dilated capillary viewed from above. A mild papillary reaction has a velvety appearance; increasing severity or chronicity may lead to enlarged, cobblestone-like papillae. Mucus and purulent material may collect within the furrows between adjacent papillae. The conjunctiva beyond the tarsus is less likely to reveal papillae because the septal connections decrease toward the fornices. With prolonged or recurrent inflammation, the septal anchors may weaken to the point at which the papillae appear reduced because of confluence. Although papillae are fairly nonspecific, they appear more commonly in cases of bacterial and allergic conjunctivitis. They are usually much less than 1 mm in diameter, but giant papillae with diameters of 1 to 3 mm may be seen in association with contact lenses, ocular prostheses, or exposed corneal sutures.

Large cobblestone papillae on the superior tarsal conjunctiva and limbal conjunctiva are common with vernal conjunctivitis. The cobblestone papillae characteristically are easily visible with eversion of the upper lid. On slit-lamp examination, they are 1 to 8 mm in diameter, have a central core of blood vessels, and stain with fluorescein at their apices from erosion during active inflammation. Laced between and on top of the giant papillae is a ropy mucoid discharge that can form a pseudomembrane. The papillae in the upper lid may become so severe as to cause a mechanical ptosis from their weight. In vernal conjunctivitis, white dots (Horner points or Trantas dots) can occur in the corneal limbus and persist for 2 days to 1 week. Follicles are not a feature of this disease. Vernal conjunctivitis can cause a reticular subepithelial fibrosis but does not cause keratoconjunctivitis sicca and only rarely causes cicatrization of the conjunctiva.[13]

Conjunctival Follicles

Lymphoid tissue is normally present within the substantia propria of the conjunctiva except in neonates, in whom follicles are not visible. Conjunctival follicles are small, elevated clusters of lymphocytes. Small follicles can be observed in the noninflamed conjunctiva, especially in the lower fornix, and clusters of noninflamed follicles have been observed in children and adolescents in a condition called *benign lymphoid folliculosis*.[14] Follicles associated with conjunctivitis are usually of recent onset, inflamed, and enlarged. Follicles used to be distinguished from papillae. Follicles have a similar elevated appearance to conjunctival papillae; however, there is no central vascular core in conjunctival follicles. The vessels surround and peripherally encroach on the raised follicle, with the central lymphocytes and other mononuclear cells often obscuring the vessels. Except in giant papillary conjunctivitis, papillae are smaller than follicles. Follicles often have a smooth, glistening surface and are most commonly seen near the tarsus, although their presence has been described on the bulbar and limbal conjunctiva.[15] As with papillae, the presence of follicles is a nonspecific sign, but follicles are most commonly associated with viral, chlamydial, and toxic conjunctivitis.

Membranes and Pseudomembranes

Membrane formation results from intertwining of the conjunctiva with coalescence of an inflammatory coagulum, forming a yellowish white membrane overlying the palpebral conjunctiva. If the fibrinous layer is intertwined with the conjunctiva via granulation tissue, it is a true membrane and will cause bleeding when removed. Pseudomembranes have a similar appearance but are not as adherent and do not bleed when removed. Viral and bacterial causes of conjunctivitis have an increased likelihood of membrane formation, although the presence of a membrane does not rule out other causes.

Conjunctival Phlyctenules and Granulomas

A phlyctenule is a whitish, nodular collection of chronic inflammatory cells located at or near the limbus, often in the center of a hyperemic area. This represents a delayed hypersensitivity reaction generally associated with *Staphylococcus* spp. or tuberculosis. However, it can also be associated with coccidioidomycosis, candidiasis, lymphogranuloma venereum, or parasitic conjunctivitis.

Although a granulomatous nodule of chronic inflammatory cells with a fibrovascular proliferation is a classic finding in Parinaud oculoglandular conjunctivitis, it is not common with most types of conjunctivitis. A conjunctival granuloma is more indicative of an embedded foreign body or a granulomatous disease (e.g., sarcoidosis, tuberculosis), but it may be seen with chlamydial and fungal conjunctivitis.

Corneal Involvement

Because of the close proximity of the conjunctiva to the cornea, it is not surprising to see extension of the conjunctival inflammation. Corneal involvement can be as mild as punctate epithelial erosions or as severe as frank ulceration that may lead to perforation. A number of bacterial agents that can cause conjunctivitis may penetrate an intact corneal epithelium. Foreign-body sensation, pain, decreased vision, and photophobia all are signs of corneal involvement; however, many of these signs are present with the inciting conjunctivitis alone. Corneal involvement, especially with viral causes, may quickly improve with the resolution of conjunctivitis; however, some associations can lead to undesired sequelae. Continued vigilance, a high index of suspicion, and appropriate treatment of corneal involvement are necessary.

Preauricular Adenopathy

The lymphatic vessels of the eyelids drain primarily to the preauricular lymph node. The medial third of the eyelids and the conjunctiva drain to the submandibular and submental lymph nodes. Preauricular adenopathy is also a nonspecific finding, but it is often present with viral, chlamydial, herpetic, and gonococcal causes of conjunctivitis and may be absent in toxic, allergic, and nongonococcal bacterial conjunctivitis. Submandibular and submental lymphadenopathy are uncommon but are usually present in Parinaud oculoglandular conjunctivitis.

LABORATORY EVALUATION

Routine laboratory evaluation is probably not performed in most cases of conjunctivitis. Although there is agreement that all cases of suspected ophthalmia neonatorum (conjunctivitis in first month of life) should have laboratory evaluation with cultures and smears for bacterial infections, nucleic acid amplification tests (NAATs) for chlamydial infections, and polymerase chain reaction (PCR) assays for herpetic infections, there is not universal agreement regarding which other cases require laboratory evaluation and which types of evaluation are most appropriate. Because most cases of conjunctivitis are viral, it is expected that most patients will experience a self-limited course, with spontaneous resolution after only supportive therapy. The patient's history and physical examination can often predict the need for laboratory evaluation. Clear cases of viral conjunctivitis may not require conjunctival scraping for stains and cultures, but if bacterial conjunctivitis is suspected, such scrapings are recommended to guide appropriate antibiotic therapy. Indiscriminate use of antibiotics without laboratory identification of a bacterial cause may lead to the emergence of resistant organisms or may aggravate the condition as the result of a toxic or immune-mediated reaction associated with the medication. Adenoviruses are responsible for 36% of conjunctivitis cases, and one report estimated that a savings of $429 million per year could be achieved if antigen testing is done before inappropriate treatment with antibiotics.[16]

The most common procedure involves the use of a calcium alginate swab or Culturette device to collect material from the conjunctiva. Material is transferred to slides for appropriate Gram and Giemsa stains and to culture plates (e.g., blood/chocolate agar, fungal media) for further identification and sensitivity testing. Diagnosis of bacterial conjunctivitis has been reviewed by Golde and Gardiner.[17] Smears from bacterial infections reveal numerous neutrophils along with the standard epithelial

and goblet cells. Lymphocytes and monocytes are predominant in viral infections. Herpetic conjunctivitis may reveal multinucleated epithelial cells and eosinophilic, intranuclear inclusion bodies. Chlamydial conjunctivitis often reveals leukocytes, lymphocytes, and epithelial cells with basophilic, intracytoplasmic inclusion bodies; these findings are noted more frequently in children than in adults. The most common agents for bacterial conjunctivitis in children are *Haemophilus influenzae* and *Streptococcus pneumoniae,*[17] whereas the most common agents in adults are *Staphylococcus aureus* and *H. influenzae.*[18] In particular, *H. influenzae* is the causative agent in children who are younger than 6 years old, and *S. aureus* is the causative agent in children older than 6 years.[19] Identification of inclusion bodies can be difficult, and suspected cases of herpes simplex virus (HSV) should have a swab sent for PCR assay. Viral conjunctivitis may be diagnosed with the use of culture, PCR assay, or immunofluorescent techniques.

VIRAL CONJUNCTIVITIS

As a group, viral organisms are probably the most common cause of conjunctivitis. Viral conjunctivitis, often called *pink eye,* is one of the most frequent reasons for a visit to the emergency department or physician's office. Because the diagnosis can usually be made clinically, viral cultures and laboratory evaluations are not commonly performed.[9] The viral organisms typically produce an acute, unilateral conjunctivitis with involvement of the second eye occurring often within 1 week. The watery discharge and conjunctival hyperemia can be quite impressive. Preauricular adenopathy is often noted on the involved side. However, it should be noted that many cases are misdiagnosed as bacterial conjunctivitis.[2] Although many health care providers prescribe antibiotics in the mistaken notion that such discharge and hyperemia have a bacterial cause, most cases of viral conjunctivitis spontaneously resolve within days to weeks, usually without adverse sequelae. Numerous viruses can cause conjunctivitis, and many can be identified by slightly differing features of the disease course.

Adenoviral Conjunctivitis

Adenoviruses are responsible for two of the most common types of conjunctivitis (see Chapter 142). These infections are spread through respiratory fomites or by direct contact with conjunctival secretions. The incubation period varies from 5 to 10 days, with the clinical process lasting 5 to 15 days.[20] Nineteen different serotypes of adenovirus have been reported to cause conjunctivitis.[21] Once the disease course passes, immunocompetent patients are protected from a recurrent adenoviral infection caused by the same serotype.

The advent of new laboratory techniques such as real-time PCR, which can identify more pathogens than routine virus isolation, has led to more accurate diagnosis of adenoviral conjunctivitis.[22] A review of the available methods for identifying adenoviruses has suggested that a commercially available immunoassay kit (RPS Adeno Detector; Rapid Pathogen Screening Inc., Sarasota, FL) using antibodies to the hexon protein may be as sensitive and ideally suited for analysis in a clinical environment.[2,23]

Although no effective treatment for viral conjunctivitis exists, some of the symptoms may be alleviated by cold compresses, topical antihistamines, and artificial tears.[24] Current antiviral medications have not been demonstrated to be useful.[25] Topical antibiotics and the use of eye droppers can complicate the clinical presentation and increase the risk of spreading the infection.[2]

Pharyngoconjunctival Fever

Pharyngoconjunctival fever has been reported to be the most common ocular adenoviral infection.[26] The most commonly implicated serotypes in pharyngoconjunctival fever are 3, 4, and 7, but it has been associated with types 1, 5, 6, and 14 as well, having been isolated from conjunctiva, nasopharynx, and feces. The incubation period after exposure is 5 to 12 days (most commonly 8 days).[27] The triad of pharyngitis, fever, and subsequent conjunctivitis is the classic clinical presentation. The conjunctivitis is marked by a follicular reaction accompanied by a mild watery discharge, hyperemia, and chemosis (edema of the conjunctiva). The cornea may have fine, punctate erosions, and preauricular adenopathy is present in about 90% of cases. The condition usually resolves spontaneously within 2 weeks. Supportive treatment with cold compresses and artificial tears is usually sufficient.

Epidemic Keratoconjunctivitis

Epidemic keratoconjunctivitis (EKC) is associated most often with adenovirus serotypes 8 and 19, but it has also been reported with multiple serotypes including types 2 to 4, 7 to 11, 14, 16, and 29. Serotypes other than 8 and 19 may produce a similar clinical picture to the latter but do not have the tendency to widespread epidemic.[27] EKC is more severe than pharyngoconjunctival fever; it lasts 7 to 21 days, with possible corneal sequelae persisting for weeks or months.[28] The mixed papillary and follicular response in the conjunctiva is accompanied by a watery discharge, chemosis, significant hyperemia, and preauricular adenopathy.[20,29] Subconjunctival hemorrhages and conjunctival membranes are found in approximately one-third of patients with EKC, especially in the more severe cases.[30] These membranes (and pseudomembranes) are made up primarily of fibrin, leukocytes, and fibroblasts. Removal of the membrane leaves a bleeding conjunctival surface; removal of pseudomembranes is not associated with such bleeding. The presence of either type of membrane can be associated with formation of conjunctival scarring and symblepharon (adhesion of conjunctival surfaces). Corneal involvement varies from almost ubiquitous diffuse, punctate epithelial elevations to subepithelial infiltrates, seen in 20% to 50% of cases, which may persist for months or longer but usually resolve without scarring or neovascularization.[29] Treatment of EKC focuses on relieving the symptoms and minimizing the spread of this highly contagious disease. Patients are usually infectious for 10 to 14 days after onset. Cold compresses, artificial tears, and possibly decongestant eyedrops constitute the main treatment. Reduced visual acuity or disabling glare from the subepithelial infiltrates often responds to topical corticosteroids.[31] Removal of the membranes and pseudomembranes, along with administration of topical steroids, often has a significant effect on patient comfort. Meyer-Rüsenburg and colleagues[32] reviewed the prevention and treatment of EKC. They recommended the application of rigorous hygienic conditions in medical facilities to reduce viral transmission.

The structural changes occurring during the course of adenovirus EKC from the onset of the disease up to 24 weeks of follow-up have been evaluated by confocal microscopy.[33] Hyperreflective cells in the basal epithelial cell layer were found 1 week after infection. Subepithelial accumulations of dendritic cells, located mainly at the level of the Bowman layer, were also observed at 1 week. Underneath the anterior stroma, clusters of highly reflective, irregularly shaped cells were detected. At 2 weeks, follicular conjunctivitis, focal keratitis, and subepithelial infiltrates were present. Confocal microscopy revealed persistent clusters of hyperreflective basal epithelial cells intermingled with roundish cells that probably represent leukocytes. Dendritic cells had formed an intricate network and, in the anterior stroma a hyperreflective cellular plaque that corresponded to the subepithelial infiltrate was detected. At 24 weeks after onset of the symptoms, density and dimension of dendritic cell clusters were decreased, but stromal hyperreflectivity in the mid-stroma was detected.[33]

Acute Hemorrhagic Conjunctivitis

Also known as Apollo 11 disease, acute hemorrhagic conjunctivitis was initially described in Ghana during the time of the first lunar landing mission in 1969.[34] The disease is associated with coxsackievirus A24 and enterovirus 70 (see Chapter 172 for nomenclature).[35] The classic presentation is rapid onset of severe, painful papillary conjunctivitis marked by chemosis, tearing, and small subconjunctival hemorrhages. Although individual hemorrhages are noted at first, these rapidly coalesce to become confluent. The resultant hemorrhagic chemosis can reach alarming proportions. The cornea may have punctate elevations or erosions, but these rarely progress to subepithelial opacities as seen with EKC. The conjunctivitis tends to clear in 4 to 6 days, but the hemorrhages may persist. Epidemics are quite common, especially in developing countries, where up to 50% of the population may be involved. Treatment again is mainly supportive.

More recent reports have documented several outbreaks of hemorrhagic conjunctivitis with coxsackievirus A24 variant.[36–38,39,40,41] Molecular serotyping methods have been reported to be a good alternative to the

gold standard cell culture–neutralization method for diagnosis in view of its easy accessibility and expected sensitivity.

Herpes Simplex Conjunctivitis

Primary ocular involvement by HSV may manifest as an acute follicular conjunctivitis or keratoconjunctivitis with preauricular adenopathy and often with notable vesiculating periocular skin involvement. Pseudomembranes may be present in the fornices. In 1% to 5% of all HSV cases, skin lesions may be absent.[2] In the absence of frank skin vesiculation, differentiation from adenoviral infection is aided by a careful search of the lid margins for signs of herpetic blistering. Conjunctival swabs should be sent for PCR assay. In contrast to primary disease, recurrent blepharoconjunctivitis is a much more localized infection. Vesicles are localized rather than diffuse, starting as red papules, which form clear vesicles, break, and scab over to heal without scarring. Virus is present in the lesions for about 3 days, although the lesions themselves take about 1 week to heal. Conjunctivitis is usually diffuse and watery. Occasionally, rose bengal or fluorescein staining reveals a conjunctival dendritic ulcer. As opposed to the host of treatment regimens used when herpetic disease affects the cornea and other ocular components, herpetic manifestations limited to the conjunctiva require minimal supportive treatment. There is no role for antiviral agents or corticosteroids; however, an antibiotic ointment such as erythromycin may be used to prevent a bacterial superinfection. Close monitoring for corneal or adnexal involvement is necessary because this complication would necessitate a change in the treatment regimen.

Research into HSV has resulted in mechanistic insights into how this virus gains entry to ocular cells and how it spreads.[42] This includes the involvement of receptors such as nectin cell adhesion molecule 1, herpesvirus entry mediator, heparan sulfate, and paired immunoglobulin-like type 2 receptor as well as the participation of Toll-like receptors and nuclear factor kappa B.[43,44] The involvement of filopodia and endocytic pathways in the initiation and progression of the disease has also been suggested.[42] The discovery that a kinase inhibitor, BX795, inhibits HSV replication is a promising alternative to use of nucleoside analogues and may have therapeutic applications.[45]

Varicella and Varicella-Zoster Conjunctivitis

Although follicular conjunctivitis and preauricular adenopathy of varicella-zoster virus are rarely seen, approximately 4% of patients with chickenpox have conjunctival or corneal findings or both.[45] Papules may be seen on the lids, conjunctiva, and limbus. Vesicles may be found on the semilunar fold and throughout the conjunctiva. The papules form pustules, which then ulcerate as the disease progresses. Again, there is no indication for antivirals or corticosteroids in this herpetic conjunctivitis. Supportive care, with the possibility of prophylactic antibacterial ointment, is usually sufficient. However, herpes zoster ophthalmicus may lead to substantial disability if left untreated.[46,47] These complications may involve the anterior segment, optic nerve, and retina, resulting in a number of ocular pathologies including optic neuritis, glaucoma, retinal vasculitis, and uveitis.[48] (See Chapter 113.)

Variola (Smallpox) Conjunctivitis

Between 10% and 20% of individuals affected with smallpox develop severe ocular complications.[49] Additionally, approximately 7% of unvaccinated patients develop corneal lesions.[50] About 5 days after the onset of clinical disease, an exanthematous, watery conjunctivitis may develop. It frequently clears without complication. However, in some patients, pustules then appear on the bulbar conjunctiva. These painful lesions are associated with a great inflammatory reaction and purulent discharge. The lesions often extend to the cornea, leading to inflammation, scarring, and possible perforation with loss of the eye. Specific treatment is currently not established. A promising but unproven treatment is systemic and topical cidofovir; this agent has some activity against variola in vitro and against poxviruses in animal model systems.[51,52] The drug tecovirimat (ST-246; Arestvyr) may prove to be useful in treating smallpox and is being stockpiled by the US government for use in the event of a bioterrorist smallpox attack (see Chapter 132). Penicillinase-resistant antimicrobial agents should be used if the skin lesions are secondarily infected or if infection is near or involves the eyes. Daily rinsing of the eyes is important in severe cases. There are no data showing that prophylaxis or treatment of variola conjunctivitis with vaccinia immunoglobulin (VIG) has any effect, but many experts would use it to reduce the likelihood of spread.

Vaccinia Conjunctivitis

The attention to smallpox as a bioterror hazard has also brought attention to the complications of smallpox vaccine (vaccinia). Lid and conjunctival involvement is the most common form of ocular vaccinia and is similar to that seen on the arm at the site of the intentional vaccination. Initial formation of vesicles progresses to indurated pustules, which then umbilicate to open sores. The resultant scab formation may occasionally scar and leave depigmented marks in the skin. Vaccinia conjunctivitis is characterized by an acute papillary reaction and serous or mucopurulent discharge. Multifocal ulceration of the palpebral and bulbar conjunctiva occurs commonly. Conjunctival ulcers have a whitish center with surrounding injection and edema; they may be covered by a thick, yellowish gray membrane and may lead to symblepharon formation. Preauricular and submandibular adenopathy commonly accompanies vaccinia conjunctivitis.[53,54] The differential diagnoses of vaccinia lesions of the eyelid or ocular adnexa include molluscum contagiosum, keratoacanthoma, bacterial blepharitis, and HSV or varicella-zoster virus infection.[55]

Clinicians must maintain a high index of suspicion for ocular smallpox vaccine–associated adverse reactions in vaccine recipients and their close contacts. Hu and colleagues[56] reported the case of a 26-year-old woman who developed right preseptal cellulitis and blepharoconjunctivitis after contact with a vaccinated member of the military. The preseptal cellulitis resolved with antibacterial therapy, and the conjunctival infection was treated successfully with a 14-day course of topical trifluridine and a single dose of intravenous VIG.[56]

Compared with historical data on the ocular complications of smallpox vaccination, the incidence of ocular complications during the Department of Defense Smallpox Vaccination program in the United States has been low. In addition, the severity of disease seems to be less than during other vaccination periods. Perhaps these findings are the result of improved screening of vaccinees, prevaccination counseling, postvaccination wound care, and the suggested efficacy of trifluridine in the treatment of ocular vaccinia.[57]

No topical antiviral agents have been approved by the US Food and Drug Administration (FDA) for the treatment of ocular vaccinia, but topical trifluridine, cidofovir, and vidarabine have been shown to be effective in animal and uncontrolled human reports. In addition, use of antiviral ophthalmic medication and VIG has been suggested.[58] VIG has been demonstrated to be effective in treatment of lid and conjunctival lesions.[59,60] A 2002 panel convened by the US Centers for Disease Control and Prevention in Atlanta recommended the treatments shown in Table 112.1 for vaccinia conjunctivitis.[61] VIG is available from the Centers for Disease Control and Prevention.

TABLE 112.1 Treatment of Vaccinia Conjunctivitis

Mild-to-Moderate Disease (Mild Hyperemia and Edema, No Membranes or Focal Lesions)
Adults: Trifluridine (Viroptic) drops 9 times daily for 2 weeks
Children: Vidarabine 3% ointment (Vira-A) 2–5 times daily for 2 weeks
A one-time dose of VIG, 100 mg/kg IM or 6000 U/kg IV, is recommended as adjunctive therapy for moderate conjunctivitis
Severe Disease (Marked Hyperemia, Edema, Membranes, Focal Lesions, Lymphadenopathy, Fever)
A single dose of VIG, 100 mg/kg IM or 6000 U/kg IV, is recommended as adjunctive therapy; repeat in 48 hours if not improved
Adults: Trifluridine (Viroptic) drops 9 times daily for 2 weeks
Children: Vidarabine 3% ointment (Vira-A) ointment 2–5 times daily for 2 weeks
Topical antibiotic to the conjunctiva to prevent secondary bacterial infection

IM, Intramuscular; *IV,* intravenous; *VIG,* vaccinia immunoglobulin.
From Centers for Disease Control and Prevention. Smallpox: Summary of October 2002 Advisory Committee on Immunization Practices Smallpox Vaccination Recommendations. *Atlanta: Centers for Disease Control and Prevention; 2002.*

Other Viral Etiologies

Rubella, rubeola, mumps, influenza, Epstein-Barr virus, papillomavirus, molluscum contagiosum, and Newcastle disease virus all have been implicated in conjunctivitis. Rubella produces a catarrhal or follicular reaction, or both, along with the typical disease findings. Influenza viruses have also been associated with a catarrhal or follicular conjunctivitis. Rubeola (measles) produces a catarrhal or papillary reaction, often with significant discomfort and photophobia. Pale, avascular spots, similar in appearance to the oral Koplik spots, can be found in the conjunctiva.[62] Patients with mumps may develop a catarrhal conjunctivitis and punctate epithelial keratitis with severe photophobia and lacrimation but often little discomfort.[63] A follicular conjunctivitis is present in about 5% of patients with Epstein-Barr–induced mononucleosis.[64] Human papillomavirus can produce lesions on the lid margin and the conjunctiva; a catarrhal conjunctivitis may follow. Molluscum contagiosum lesions on the lid margin may cause an irritating chronic follicular conjunctivitis with punctate keratitis, superior corneal vascular pannus, and cicatricial punctal occlusion. Lesions may also occur several millimeters away from the lid margins yet still cause a follicular conjunctivitis with culture positive for virus.[65] Lesions confined only to the cornea or conjunctiva are rare but not unknown. They are usually seen in patients with immune dysfunction.[66] Newcastle disease, seen primarily in poultry workers, veterinarians, and laboratory technicians, typically produces a unilateral, follicular, and papillary conjunctivitis with hyperemia, edema, and chemosis usually in the lower fornix, mild tearing, and preauricular adenopathy.[67] Poultry workers may develop conjunctivitis from poultry infected with avian influenza viruses such as one outbreak of 78 patients with H7N7 conjunctivitis.[68]

In all of these cases, there is no specific therapy directed toward the conjunctivitis because it is almost always self-limited. Therapy directed toward the causative agent (e.g., removal of molluscum lesions) may hasten resolution of the conjunctivitis.

CHLAMYDIAL CONJUNCTIVITIS

Chlamydia trachomatis Infection

Chlamydial infections cause several important acute and chronic eye infections.[69] Studies using monoclonal antibodies to the chlamydial major outer membrane protein have identified several serotypes of *Chlamydia trachomatis.* Serotypes B, Ba, and D through K, which are often sexually transmitted, can cause a follicular conjunctivitis in an adult (inclusion conjunctivitis). The same serotypes can lead to neonatal conjunctivitis if an infected mother transmits the pathogen to the newborn during vaginal delivery. NAATs, used for genital specimens, are also useful for ocular samples.[70] Repeated infections with *C. trachomatis* serotypes A, B, Ba, and C can cause trachoma, a chronic follicular keratoconjunctivitis that remains the most common cause of preventable blindness in the world. *C. trachomatis* infection can also cause acute reactive arthritis (formerly known as Reiter syndrome),[71] a triad of urethritis, arthritis, and iridocyclitis frequently seen in sexually active young men who are positive for the HLA-B57 histocompatibility allele. In addition, several cases of Parinaud oculoglandular syndrome have been reported with lymphogranuloma venereum, a sexually transmitted disease characterized by painful inguinal lymphadenopathy and caused by *C. trachomatis* serotypes L1 through L3. Although vaccines for chlamydial infections have been developed for animals, such vaccines have not yet been generated for humans. Strategies and promising avenues for development of vaccines for chlamydial infections in humans have been summarized elsewhere.[72] Treatment with systemic antibiotics such as doxycycline and oral azithromycin of both patients and sexual partners is recommended.[24]

Chlamydia pneumoniae Infection

Chlamydia pneumoniae shares considerable homology with *C. trachomatis* and follows a similar life cycle.[72] However, it is transmitted by aerosol droplets; it can target a spectrum of cell types; and it is associated with several chronic inflammatory diseases, most notably atherosclerosis.[73] Although *C. pneumoniae* first was isolated from the conjunctiva, there are few studies on its role in ocular disorders. The organism has been detected in conjunctival swabs collected from patients with conjunctivitis,[74] but a clear association with external ocular disease is lacking. Although it has been suggested that there is an association of *C. pneumoniae* with age-related macular degeneration,[75] most evidence indicates the lack of association of *Chlamydia* infection with age-related macular degeneration.[76]

Trachoma

C. trachomatis serotypes A through C are responsible for trachoma. Active trachoma affects an estimated 84 million people; another 7.6 million have end-stage disease, of which about 1.3 million are blind.[77] The severely blinding condition is endemic in many developing countries, especially in areas of close overcrowding and poor sanitation. Trachoma is typically the result of multiple untreated infections rather than a one-time event. In some trachoma-endemic communities in the Solomon Islands, clinical signs of active trachoma are associated with nonchlamydial microbial species of several types such as *S. aureus*, Adenoviridae, coagulase-negative *Staphylococcus, H. influenzae, Moraxella catarrhalis,* and *S. pneumoniae.*[78] The initial follicular conjunctivitis begins in the upper palpebral conjunctiva and is followed by limbal follicles. Papillary hypertrophy, mucopurulent discharge, superior corneal pannus (neovascularization), and epithelial keratitis are early features of the disease. Later stages are marked by cicatrization of the conjunctiva, cornea, and eyelids.

Trachoma stands on the brink of extinction thanks to a 1998 initiative launched by the World Health Organization (WHO) entitled the WHO Alliance for the Global Elimination of Trachoma by 2020. This program advocated control of trachoma at the community level with four interrelated population health initiatives that form the *SAFE* strategy: *s*urgery for trichiasis, *a*ntibiotics for active trachoma, *f*acial cleanliness, and *e*nvironmental improvement. Evidence supports the effectiveness of this approach, and if current world efforts continue, blinding trachoma will indeed be eliminated by 2020.[79,80] In this context, the success of this approach has been demonstrated by the elimination of trachoma in Nepal.[81] As of 2017, 10 of 41 endemic countries have reported elimination of trachoma.[82] It has been suggested that the SAFE strategy be expanded to include sexual ecosystem and behavioral valuation/education, resulting in the acronym *SAFES.*[83]

The blinding complications of trachoma are the result of corneal exposure and ulceration caused by conjunctival scarring and lid deformities.[84] Two classic findings are Arlt line and Herbert pits. Arlt line is a horizontal line of conjunctival scarring found along the superior palpebral conjunctiva. Herbert pits are sharply demarcated erosions near the limbus that are filled with epithelium after the cicatrization of the limbal follicles. Once regression of the superior pannus occurs, a diffuse corneal haze may be seen. Eyelid deformities are the result of conjunctival scarring. Lids can be turned inward (entropion) or outward (ectropion), and lashes can be directed against the cornea (trichiasis), all of which contribute to an irregular ocular surface. Such irregularities can cause corneal scars, ulcers, neovascularization, and perforation. Certain interventions have been shown to be more effective at eliminating trichiasis. Full-thickness incision of the tarsal plate and rotation of the lash-bearing lid margin was found to be the best technique and preferably delivered in the community.[85]

Most trachoma programs use the WHO simplified grading system, which was specifically designed to allow rapid assessment of prevalence and severity of disease within a population. The grading system is based on the presence or absence of five clinical signs, as follows:[79]

- Trachomatous inflammation follicular: five or more follicles of larger than 0.5 mm on upper tarsal conjunctiva
- Trachomatous inflammation intense: inflammatory thickening obscuring more than half the normal deep tarsal vessels
- Trachomatous conjunctival scarring: presence of easily visible scars in the tarsal conjunctiva
- Trachomatous trichiasis: at least one eyelash rubbing on the eyeball or evidence of recent removal of in-turned eyelashes
- Corneal opacity: corneal opacity blurring part of pupil margin

Although there is no gold standard test for *C. trachomatis,* it has been determined that a clustered latent class analysis using WHO criteria and PCR assay may provide a useful method for diagnosis.[86]

Systemic tetracycline or erythromycin has been given for 3 to 4 weeks. Because the clinical response can often take several months,

topical tetracycline or erythromycin is often used twice daily for 5 days each month for 6 months.[21] This repeated topical treatment is especially useful in situations in which repeat infection is likely. Loosely based on the smallpox eradication efforts, widespread prophylactic systemic antibiotics have been tried in endemic areas in an attempt to eliminate the disease. A single dose of azithromycin was proposed as a good choice for the eradication theory.[87] The use of azithromycin for 3 to 5 days has also been proposed for treatment in patients with bacterial or trachomatous conjunctivitis.[88] With the advent of topical azithromycin, there has been support for consideration of using this eye drop as a treatment for the various ocular sequelae of trachoma.[89] Evidence has been provided that face washing alone or in combination with treatment with topical tetracycline is ineffective in treatment of active trachoma.[90]

Consensus has built on the value of mass treatment strategies for both logistic and efficacy reasons. Important unanswered questions remain about the best distribution strategies including timing of repeat mass antibiotic treatment and duration of treatment. Theoretical models suggest that biannual treatment is necessary when the baseline prevalence is greater than 50% in children. WHO currently recommends mass treatment for at least 3 years if the prevalence of trachoma in children 1 to 9 years of age is greater than 10% and then reassessment of prevalence. Evidence to guide duration of treatment is scarce; however, trachoma is unlikely to be eliminated until the SAFE strategy has been implemented for at least 3 years. A survey was published in 2012 on the clinical management, treatment options, and challenging issues facing elimination of this disease.[91]

Adult Inclusion Conjunctivitis

C. trachomatis can cause a chronic follicular conjunctivitis in adults and neonates. The adult form is usually sexually transmitted, with an estimated 1 in 300 patients with genital chlamydia developing conjunctivitis,[92] but it can occur with orogenital or hand-to-eye transmission of secretions.[93] The most common presentation comprises a unilateral red eye (although it can be bilateral), preauricular adenopathy, papillary hypertrophy, marked hyperemia, mucopurulent discharge, and a follicular reaction. Men often have a concomitant urethritis; women may have chronic cervicitis. Corneal involvement may quickly follow conjunctivitis resulting in punctate keratitis, EKC-like infiltrates, and superior limbal pannus (neovascularization). Corneal scarring and neovascularization are less common with inclusion conjunctivitis than with trachoma, and the upper and lower palpebral conjunctivae are often equally involved, as opposed to the preferentially affected upper conjunctiva in trachoma. However, severe inclusion conjunctivitis may be associated with a chronic, relapsing course leading to characteristics generally seen in trachoma.

Treatment of Adult Inclusion Conjunctivitis

Because of the prominent sexual transmission of this form of conjunctivitis, it is important to simultaneously treat all known sexual partners. Failure to do so often results in more serious sequelae associated with reinfections. Topical antibiotics are relatively ineffective, so systemic therapy is the mainstay of treatment. Tetracycline, doxycycline, or erythromycin is given for 3 weeks, with caution to avoid tetracycline in young children and in pregnant or lactating women. The use of oral azithromycin was found to be effective in the treatment of *Chlamydia* infection, although often more than one course of treatment was required.[94]

Lymphogranuloma Venereum

Certain serotypes of *C. trachomatis* (L1, L2, and L3) have been associated with systemic lymphogranuloma venereum. The associated conjunctivitis is often mild and unilateral, producing a scant, watery discharge. Although the conjunctivitis appears mild, there is impressive edema in the upper and lower eyelids. In addition to the usual preauricular lymphadenopathy, the nodes in the parotid and submaxillary region are also involved. There is a report of lymphogranuloma venereum conjunctivitis causing a keratitis leading to a corneal perforation in a patient with acquired immunodeficiency syndrome.[95] Treatment is similar to that for inclusion conjunctivitis.

BACTERIAL CONJUNCTIVITIS

There is significant disagreement on the actual incidence of bacterial conjunctivitis. Many cases of conjunctivitis are treated as if they were caused by bacterial organisms, but culture-proven bacterial conjunctivitis appears uncommon. The clinical presentation is characterized by a rapid onset of unilateral lid edema, conjunctival injection, and a mucopurulent discharge, followed by involvement of the second eye within 1 to 2 days. *Staphylococcus* spp. and *Corynebacterium* spp. are the most common organisms to colonize the lids and conjunctiva; consequently they are prominent causes of infectious conjunctivitis.[96] Although almost any bacterial organism can cause conjunctivitis given the appropriate set of conditions, the most common ones are *Staphylococcus* spp., *S. pneumoniae, Haemophilus* spp., *Moraxella, Corynebacterium diphtheriae, Neisseria* spp., and enteric gram-negative rods.[97] Wearing contact lenses has also been associated with changes in the ocular conjunctiva, making it more similar to that of the skin microbiota and that may influence the development of conjunctivitis.[98] The prevalence of microbial contamination in counterfeit and decorative contact lenses has also been reported.[99] Cases of contact lens care solution contamination by histamine-producing *Raoultella* spp. is also reported to cause keratoconjunctivitis.[100,101]

Pathogenesis

The pathogenesis of bacterial conjunctivitis usually involves a compromised epithelial surface. Although intact epithelium is an effective barrier to most organisms, *Neisseria gonorrhoeae, C. diphtheriae, Haemophilus aegyptus* (Koch-Weeks bacillus), and *Listeria monocytogenes* can penetrate such a surface through specialized attachments or toxins or both.[102] Injured epithelium or specialized attachments allow adhesion, which may result in the entry of various bacterial products and toxins. Enzymatic components such as proteases, coagulases, collagenases, and fibrinolysins combined with toxins such as those seen in *Staphylococcus* spp. and *Pseudomonas* spp. can disrupt underlying tissue, allowing further bacterial entry and possible isolation from host defense mechanisms.[103] Bacterial conjunctivitis can be clinically categorized as acute, hyperacute, or chronic on the basis of various features.

Acute (Mucopurulent) Bacterial Conjunctivitis

S. aureus, S. pneumoniae, and *H. influenzae* are the organisms that most commonly cause bacterial conjunctivitis. The acute conjunctivitis is marked by unilateral hyperemia, tearing, mucopurulent discharge, and matting of the eyelids. *S. aureus* is the most common agent in adults and children; *S. pneumoniae* and *H. influenzae* occur more frequently in children than in adults.[104] *H. influenzae* is often associated with systemic infections such as upper respiratory tract disease, and its treatment usually requires administration of systemic antibiotics. Viridans streptococci and *Streptococcus pyogenes* can produce an acute conjunctivitis, often with an associated membranous reaction. Gram-negative rods, other than *Haemophilus* spp., rarely cause acute conjunctivitis in immunocompetent patients.

Treatment of Acute Bacterial Conjunctivitis

Appropriate laboratory confirmation of bacterial conjunctivitis should be attained to guide treatment. Although many mild conjunctival infections resolve on their own, topical antibiotic treatment may speed resolution and reduce severity and morbidity.[105] Although topical antibiotics reduce the duration of the disease, comparison of outcomes between treatment and placebo groups showed little difference.[106] Treatment with a topical broad-spectrum agent such as sulfacetamide, trimethoprim-polymyxin B, or a fluoroquinolone is given for 7 to 10 days. Topical moxifloxacin has gained FDA approval to treat bacterial conjunctivitis in patients as young as 3 years of age, and topical azithromycin has been shown to be effective in treating bacterial conjunctivitis with a 3-day course.[107] Appropriate agents may be selected or altered on the basis of laboratory results. In cases of pediatric bacterial conjunctivitis (<1 year of age), erythromycin is the preferred antibiotic because of its decreased side effects.[108] However, there is greater resistance to erythromycin, and so fluoroquinolone may be a good choice because it has the lowest resistance rates regardless of the patient's age.[19]

In one study it was reported that the upper eyelid may have tarsoconjunctival crypts, and these may be a reservoir for the organisms. It was recommended that marsupialization of the crypts be performed because it obliterates the potential space and was found to be curative.[109]

Hyperacute (Purulent) Bacterial Conjunctivitis

The most frequent cause of hyperacute conjunctivitis is *N. gonorrhoeae;* a less severe form can be seen with *Neisseria meningitidis.*[110] This severe disease is most common in neonates, sexually active adolescents, and young adults. The most impressive characteristic is the copious, thick, yellowish green, purulent discharge. Marked chemosis, painful hyperemia, and eyelid edema are seen. In contrast to most cases of bacterial conjunctivitis, there is often tender preauricular adenopathy. There may be conjunctival membrane formation, and the condition may rapidly progress to corneal ulceration and perforation because *Neisseria* spp. can penetrate an intact corneal epithelium in as little as 24 hours.

Treatment of Hyperacute Bacterial Conjunctivitis

Laboratory evaluation via Gram stain and culture is important because the treatment of *Neisseria* conjunctivitis is different than that of most bacterial entities. Topical antibiotics can augment treatment, but systemic therapy is the mainstay with *Neisseria* infections. The prevalence of penicillin-resistant organisms has made ceftriaxone the treatment of choice. Gonococcal conjunctivitis without corneal involvement may be treated with one intramuscular injection of ceftriaxone. Corneal involvement usually requires hospitalization for a 3-day course of intravenous treatment. Topical antibiotic ointments and solutions have been considered, but the most important topical therapy is frequent (every 30–60 minutes) saline irrigation of the conjunctival surface and fornices to remove the inflammatory cells, proteolytic enzymes, and debris, which may be toxic to the ocular surfaces. Because up to one-third of patients with gonococcal conjunctivitis have been reported to have *Chlamydia,* concurrent treatment with tetracycline, doxycycline, or azithromycin may be indicated. A 1.5% azithromycin solution was found to be well tolerated and effective in patients with purulent bacterial conjunctivitis.[90]

Chronic Bacterial Conjunctivitis

The most common causes of chronic bacterial conjunctivitis are *Staphylococcus* spp.[111] Such infections can be difficult to eradicate because the eyelid margins and surrounding skin are heavily populated with staphylococci. Associated exotoxins are thought to be responsible for the effect on the conjunctiva, lids, and cornea. A diffuse hyperemia, minimal mucopurulent discharge, and conjunctival thickening with either a follicular or a papillary reaction are common. Eyelid involvement may manifest as redness, telangiectasia, loss of lashes, thickening, or recurrent hordeolum (stye), and ulceration at the base of the eyelashes may be seen. Maceration and ulceration of the inner and outer canthal angles may be seen in chronic blepharoconjunctivitis caused by *Moraxella* spp. Chronic staphylococcal blepharoconjunctivitis may lead to marginal corneal ulceration, most likely as a result of an immune-mediated hypersensitivity reaction. Gram-negative bacteria are more common in chronic conjunctivitis than acute conjunctivitis.[112] Organisms more often associated with the intestinal flora can be associated with chronic conjunctivitis. *Proteus mirabilis* is the most common of these, but *Klebsiella pneumoniae, Escherichia coli,* and *Serratia marcescens* have also been described.

Treatment of Chronic Bacterial Conjunctivitis

Treatment of chronic bacterial conjunctivitis demands appropriate antibiotic therapy combined with aggressive lid hygiene and possible evaluation of the lacrimal system. Laboratory evaluation may guide appropriate antibiotic treatment, often with erythromycin or bacitracin ointment. Lid hygiene involves the use of warm compresses, eyelid scrubs with nontearing shampoo, and gentle lid massage because the meibomian (sebaceous gland) orifices at the base of the eyelashes may harbor the inciting agents. The lacrimal canaliculus or sac may also serve as a bacterial reservoir requiring antibiotic irrigation and oral antibiotics. The staphylococcal hypersensitivity reaction in the cornea may require mild topical corticosteroid treatment to reduce the associated inflammation. Oral tetracycline or doxycycline may be beneficial in more severe infections.

NEONATAL CONJUNCTIVITIS

Any conjunctivitis occurring within the first 4 weeks of life is classified as neonatal conjunctivitis (ophthalmia neonatorum).[113] A mucoid discharge in the corner of the eye and persistent tearing are typical symptoms. Conjunctivitis in the newborn can be bacterial, viral, chlamydial, or toxic (reaction to chemicals). Specific identification of the cause is particularly important because there is often a potentially serious systemic infection associated with the localized ocular condition. Neonatal conjunctivitis is more commonly found if infants are delivered vaginally compared with cesarean delivery, and this may be a risk factor for this disease.[114] The cause, properties of the eye discharge, and suggested treatment are summarized in Table 112.2.

Neonatal Chemical Conjunctivitis

In 1881 Credé introduced the use of topical silver nitrate as prophylaxis against neonatal gonococcal infection.[115] The self-limited conjunctivitis, present in approximately 90% of treated newborns, usually begins a few hours after delivery and resolves in 24 to 36 hours.[116] Although quite effective against *N. gonorrhoeae,* silver nitrate has little effect on bacteria and essentially no effect on chlamydia or viruses.[117] Silver nitrate may injure epithelial cells to such a degree that they are more susceptible to the entry of other microbial agents. Silver nitrate may still be used in some countries, but hospitals in the United States have changed to

TABLE 112.2 Etiology and Treatment of Neonatal Conjunctivitis Based on Time Frame of Symptoms

TIME FRAME OF SYMPTOMS	TYPICAL CAUSE	TYPE OF EYE DISCHARGE	TREATMENT
1–24 h	Chemical		No treatment required; resolves within 2–4 days
24–48 h	*Neisseria gonorrhoeae*	Profuse, purulent	Topical irrigation with saline, IV ceftriaxone; topical atropine if corneal involvement; neonate, mother, and sexual partner should be treated for chlamydia as well
2–5 days	Gram-positive organism (e.g., *Staphylococcus aureus*)	Purulent	Bacitracin ointment for 2 weeks
5–14 days	*Chlamydia trachomatis*	Watery, followed by purulent and bloody	Erythromycin drops qid plus erythromycin suspension for 2–3 weeks or azithromycin for 3 days
6–14 days	HSV	Watery	Topical vidarabine ointment plus systemic acyclovir
5–18 days	*Pseudomonas aeruginosa*	Greenish	Gentamicin, tobramycin, or ciprofloxacin qid for 2 weeks

HSV, Herpes simplex virus; *IV,* intravenous.
Data from Neonatal conjunctivitis. https://en.wikipedia.org/wiki/Neonatal_conjunctivitis; and Makker K, Kaufman EJ. Conjunctivitis, Neonatal. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2018.

erythromycin or tetracycline ointment. Povidone-iodine (Betadine) is markedly inexpensive and quite effective against many microbial agents; it is becoming more widely used as a prophylactic agent for newborns, especially in developing countries. The associated chemical conjunctivitis is similar in nature and course as that seen with silver nitrate. Liquid detergent capsules have also been associated with ocular conjunctivitis in children in a study from the United Kingdom.[118]

Neonatal Chlamydial Conjunctivitis

The most frequent cause of neonatal conjunctivitis in the United States is *C. trachomatis.*[119] Up to 3 million new cases of chlamydial infection occur annually,[120] with 4% to 10% of all pregnant women in the United States being diagnosed with chlamydia.[121] The infant of an untreated mother has a 30% to 40% chance of developing conjunctivitis and a 10% to 20% chance of developing pneumonia.[115] A unilateral or bilateral discharge begins 5 to 14 days after delivery. NAATs have been demonstrated to be more sensitive than other conventional methods in detecting neonatal chlamydial conjunctivitis and may be useful for the routine screening and treatment of genital *C. trachomatis* infection in pregnant women.[122–124]

Chlamydial conjunctivitis in the neonate differs from chlamydial conjunctivitis in the adult in a number of ways. No follicular response is seen in the neonate because of the inability of the immature immune system to form such a reaction. The amount of mucopurulent discharge is greater in the neonate, as is the propensity to form membranes on the palpebral conjunctiva. The infection in neonates is more responsive to topical medications. Although the typical conjunctivitis is mild and self-limited, severe cases can result in conjunctival scarring with corneal pannus and scarring. If erythromycin or tetracycline ointment is applied to the conjunctival surface within 1 hour after delivery, the chance of developing chlamydial conjunctivitis is reportedly almost zero.[125] However, topical medications cannot treat the pneumonitis and otitis media that may accompany the conjunctivitis. In a newborn with laboratory-proven chlamydia conjunctivitis, 2 weeks of oral erythromycin therapy is given; a second course may be given if adequate resolution is not achieved with the initial treatment. The mother and her sexual partners must also be treated with oral erythromycin or tetracycline (with caution in breastfeeding mothers) for 1 week.

Neonatal Gonococcal Conjunctivitis

The incidence of neonatal gonococcal conjunctivitis has decreased dramatically with effective prenatal screening and use of prophylactic antimicrobial agents in newborns. The clinical presentation begins with a hyperacute bilateral conjunctival discharge that appears within the first 24 to 48 hours after delivery. The associated purulent exudate is often so profuse that it reappears immediately after cleaning of the eye. Conjunctival membrane formation is not uncommon. *N. gonorrhoeae* can penetrate an intact epithelial surface and quickly invade the cornea, causing ulceration, perforation, and endophthalmitis if not promptly treated. Other localized gonococcal infections such as rhinitis and proctitis may be present as well as the rare but more severe disseminated infection with arthritis, meningitis, pneumonia, and septicemia, which could lead to infant death.[120] With resistance emerging against penicillin, tetracycline, and the fluoroquinolones, a single dose of intramuscular or intravenous ceftriaxone, 25 to 50 mg/kg, not to exceed 125 mg, is the preferred treatment.[126] Hospitalization and hourly saline irrigation of the conjunctival fornices are recommended; if corneal involvement cannot be ruled out because of the copious exudation, topical antibiotics are applied.[127] Povidone-iodine prophylaxis treatment has also been suggested, but its effectiveness compared with tetracycline ointment has been questioned.[128–130] Fusidic acid may prove to be a promising treatment.[131]

Nongonococcal Neonatal Bacterial Conjunctivitis

Numerous organisms can cause bacterial conjunctivitis in the newborn. Most infections are associated with gram-positive organisms such as *Staphylococcus* spp. and *Streptococcus* spp. Gram-negative organisms such as *Haemophilus* spp. and *Enterobacter* spp., *E. coli, P. mirabilis, K. pneumoniae,* and *S. marcescens* have been less commonly implicated.[132] Although *Pseudomonas aeruginosa* is a rare cause of neonatal conjunctivitis, it warrants special consideration because of its ability to rapidly cause corneal ulceration and possible perforation.[133]

Although symptoms can manifest at any time within the first month of life, nongonococcal bacterial conjunctivitis usually manifests 2 to 5 days after delivery. The clinical presentation consists of periorbital edema, chemosis, and conjunctival hyperemia and discharge. There is a higher incidence if obstruction of the nasolacrimal system is present. Conjunctival scraping for Gram stain and cultures allows for appropriate treatment—usually erythromycin ointment for gram-positive organisms and either gentamicin or tobramycin ointment for gram-negative organisms.

Neonatal Viral (Herpetic) Conjunctivitis

Herpetic conjunctivitis in the neonate is rare but can be associated with significant morbidity and mortality. HSV types 1 and 2 can be associated with conjunctivitis. In theory HSV-1 can be transmitted to the infant through oral secretions from an adult or sibling with an active cold sore, but the more common source is contact with HSV-2 during passage through an infected birth canal. Edema, conjunctival injection, and tearing usually begin within the first 2 weeks of life and may be followed by keratitis or keratouveitis. Diagnosis is commonly made by Giemsa stain but can be confirmed in 24 to 48 hours by PCR assay. If HSV is detected in neonatal conjunctivitis, the infant should be evaluated for extent of HSV infection, and intravenous acyclovir should be started immediately per American Academy of Pediatrics guidelines.[82]

PARINAUD OCULOGLANDULAR CONJUNCTIVITIS

Parinaud oculoglandular conjunctivitis refers to the association of follicular conjunctivitis and unilateral preauricular lymphadenopathy. This classification describes a type of conjunctivitis that has numerous associated causes including bacterial, viral, parasitic, mycobacterial, syphilitic, leukemic, and fungal agents. Red eye, mucopurulent discharge, and foreign-body sensation are accompanied by one or more granulomatous nodules on the palpebral conjunctiva. There is usually a visibly enlarged preauricular or submandibular lymph node on the involved side. This follicular conjunctivitis is associated with a fever and possible skin rash. *Bartonella henselae,* or cat-scratch disease, is the most common cause, but tularemia, tuberculosis, syphilis, lymphoma, mumps, Epstein-Barr virus, sporotrichosis, and sarcoidosis all have been implicated as potential causes.

Cat-scratch disease often resolves spontaneously, but 1 month of topical and systemic antibiotic therapy has been described. Because of the host of etiologic agents, an extensive workup may be warranted, with the identified cause given the appropriate systemic treatment (see Chapter 234).

PARASITIC CONJUNCTIVITIS

Leishmaniasis

A number of parasites may be associated with conjunctivitis, either by primary infection or secondarily as a response to the presence of the parasite. Blepharoconjunctivitis caused by *Leishmania* may begin as simple edema and hyperemia, with eventual progression to superficial phlyctenules in the conjunctiva and at the corneal limbus.[134] These phlyctenules may progress to abscess formation, scarring of the lids and conjunctiva, and corneal perforation. These parasites are obligate intracellular agents that are transmitted through bites of infected sand flies.

Other Parasites and Ectoparasites

The tsetse fly can infect humans with the flagellates responsible for African trypanosomiasis or sleeping sickness. Ocular effects manifest as unilateral conjunctivitis, periorbital edema, and preauricular lymphadenopathy.[135] Cryptosporidia, fly larvae, and nematodes (e.g., *Loa loa*) have also been implicated as parasitic causes of conjunctivitis.[136,137,138–140] The lid margin and lashes may be colonized by *Phthirus pubis* (lice) or *Demodex* (mites), with conjunctivitis occurring as a reaction to the organism or its waste products. Treatment for the actual conjunctivitis associated with the parasitic agents is mainly supportive;

more aggressive treatment may be necessary for the systemic parasitic condition.

FUNGAL CONJUNCTIVITIS

Although various fungal agents can be recovered from the conjunctiva, fungal conjunctivitis is rarely observed clinically. Compared with fungal keratitis, relatively few organisms have been implicated in fungal conjunctivitis. *Candida* spp., *Blastomyces* spp., and *Sporothrix schenckii* have been associated with a granulomatous conjunctivitis. These mycoses are treated with systemic antifungal agents. Conjunctival *Rhinosporidium seeberi* infection usually manifests as a fleshy, friable, red, pedunculated mass.[1] Excision of the mass with adequate margins is often curative.

Microsporidia are ubiquitous obligate intracellular fungi that are found more often in animal hosts, but the related microsporidian, *Encephalitozoon,* has been implicated as the cause of a mild conjunctivitis with punctate epithelial keratitis in immunocompromised patients.[135] *Vittaforma corneae* can cause keratoconjunctivitis in immunocompetent individuals and was responsible for a large case cluster in rugby players, probably contracted from mud splattered over their faces.[141] Symptoms of conjunctivitis may be mild and can easily be mistaken for tear film deficiencies or blepharitis; a high index of suspicion is required to make a clinical diagnosis of microsporidial conjunctivitis. Modified trichrome is a useful stain for demonstrating the organisms in smears. Oral albendazole, 400 mg twice daily, has been reported to be effective (see Chapter 43). Topical fumagillin can be obtained as Fumidil B and formulated for human use but is not approved by the FDA; fumagillin has been used to successfully treat microsporidial keratoconjunctivitis (see Chapter 270).[136] In general, medical treatment in immunocompromised patients involves long duration with frequent recurrences after discontinuation of medication.

NONINFECTIOUS VISION-THREATENING CONDITIONS ASSOCIATED WITH RED EYE

Care must be taken with any patient who presents with a red eye because there are numerous conditions that can simulate conjunctivitis including dry eye, blepharitis, endophthalmitis, cellulitis, carotid cavernous fistula, anterior segment tumors, scleritis, and subconjunctival hemorrhage.[142] As with most conditions, a thorough medical history and physical examination are helpful in the differential diagnosis. Most cases of conjunctivitis are associated with fairly painless discharge and irritation, essentially normal vision, normally reactive pupil, normal intraocular pressure, essentially clear cornea, and generally diffuse conjunctival injection. Three possible sight-threatening conditions—angle-closure glaucoma, uveitis, and corneal ulcer—often have different signs, which may enable a more proper diagnosis.

An attack of angle-closure glaucoma is associated with significant pain, often nausea, usually no discharge, generally markedly decreased vision, middilated nonreactive pupil, markedly elevated intraocular pressure, a cloudy and edematous cornea, and a more localized conjunctival injection in the limbal region. Uveitis is generally associated with mild-to-moderate pain with photophobia, essentially normal to mildly reduced vision, no discharge, a small–to–normal-sized reactive pupil, normal-to-low intraocular pressure (elevated in herpetic uveitis and Posner-Schlossman syndrome), a generally clear cornea, and a localized conjunctival injection around the limbus. Corneal ulcers are quite painful and are usually accompanied by moderately to markedly reduced vision, variable mucoid or mucopurulent discharge, normally reactive pupil, normal intraocular pressure, an opaque lesion that is easily visible in the cornea, and a generalized conjunctival injection.

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113 Microbial Keratitis

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SHORT VIEW SUMMARY

Definition
- Microbial keratitis is a vision-threatening corneal inflammatory condition caused by bacteria, viruses, fungi, or parasites.

Epidemiology
- Disease burden is higher in developing than in developed countries.
- Risk factors include contact lens wear, trauma (surgical and nonsurgical), contaminated ocular medications, altered structure of the corneal surface, and contributing systemic diseases.
- Contact lens use is the main cause for keratitis in the United States: poor lens storage and hygiene, and extended-wear use.
- Nonsurgical ocular trauma is the main cause of keratitis in developing countries.
- Trachoma is encountered more commonly in developing countries.

Microbiology
- Pathogens can be gram-negative organisms, such as *Pseudomonas aeruginosa*.
- Pathogens can be gram-positive organisms, such as *Staphylococcus* and *Streptococcus* spp.
- Viral pathogens include herpes simplex virus, varicella-zoster virus, and adenovirus.
- Outbreaks of microbial keratitis in contact lens wearers have involved *Acanthamoeba* and *Fusarium* spp.

Diagnosis
- Symptoms include severe pain and discomfort, tearing, photophobia, blepharospasm, and decreased vision.
- Clinical presentation includes conjunctival injection and discharge, decreased corneal transparency, corneal infiltrate, epithelial defect and/or stromal inflammation, corneal edema, corneal neovascularization, stromal melting, and loss of vision.
- Knowing the nature of the stromal inflammation (suppurative or nonsuppurative) and its location (focal, multifocal, or diffuse) is helpful.
- Corneal scrapings and cultures should be performed on all suspected cases of infectious keratitis.

Therapy
- Aggressive antimicrobial therapy should be initiated after scrapings and cultures of infectious keratitis.
- Fortified topical administration is the most common route of antimicrobial therapy. Subconjunctival injections, parenteral and oral routes, and antibiotic-soaked collagen shields/soft lenses are used infrequently.
- Fortified cefazolin and aminoglycoside should be used for more severe bacterial keratitis.
- Monotherapy with a fourth-generation fluoroquinolone, such as moxifloxacin, is used for bacterial keratitis.
- Antifungal therapeutic agents include topical natamycin, amphotericin B, flucytosine, fluconazole, voriconazole, and itraconazole. Oral itraconazole and voriconazole have also shown favorable outcomes when added to topical therapy. Keratoplasties are performed in recurring and unresolved keratitis.
- Novel therapies continue to develop to mitigate drug resistance problems.

Keratitis is an inflammation of the cornea produced by infectious organisms or noninfectious agents or stimuli. Microbial keratitis is a potentially vision-threatening infectious corneal inflammation event that can be caused by bacteria, viruses, fungi, or parasites.[1] Microbial keratitis is a significant public health problem. Each year in the United States, 930,000 clinic visits and 58,000 emergency department visits are due to keratitis and conditions caused by contact lens wear, which cost $175 million in direct health care expenditures and occupy over 250,000 hours of clinician time.[2] Additionally, keratitis accounted for 7.7% of medical conditions associated with hospitalization for corneal ulcers. Fungal ulcers are reported to have worse clinical outcomes than the bacterial ones because no new treatments have been introduced since topical natamycin in the 1960s.[3,4] Infectious keratitis also causes corneal opacities, which are reported to be responsible for 10% of avoidable visual impairment in some of the world's least developed countries.[5,6] Contact lens–related microbial keratitis is on the rise and may be associated with severe infections and loss of vision.[7] Specifically, the incidences of *Acanthamoeba* and fungal infections are on the rise.[8] Studies have shown that the environment also plays a role. In developing countries and tropical countries, bacterial keratitis is decreasing whereas fungal keratitis cases are also increasing.[9] In temperate countries such as the United Kingdom, bacterial keratitis accounts for 90% of the cases. Infectious keratitis requires prompt diagnosis and expedient treatment to prevent blindness or even enucleation. There are few clinical signs that distinguish microbial keratitis from corneal inflammation associated with trauma, hypersensitivity, or immune-mediated conditions. The patient's history and ocular examination, focusing on the presence or absence of an epithelial defect and/or stromal inflammation, serve as important diagnostic clues. The nature of the stromal inflammation (suppurative or nonsuppurative) and its location (focal, multifocal, or diffuse) are also helpful in making a diagnosis. Microbiologic tests are needed to establish the etiologic agent and antimicrobial susceptibility, but therapy is often begun before these results are final.

Given the rapid progression and virulent nature of many infectious agents, any corneal inflammation should be considered a threat to vision, requiring prompt evaluation and treatment. Even relatively minor corneal ulcerations may lead to significant reduction in visual acuity, should they be located on the visual axis. Corneal perforation can occur in as little as 24 hours with certain virulent organisms; subsequent endophthalmitis (inflammatory process involving the ocular cavity and adjacent structures), leading to loss of vision or even loss of the eye, is an ever-present danger in such settings.

ETIOLOGIC AGENTS AND RISK FACTORS

Microbial Agents

The conjunctival surface has been theorized to be the location of hundreds of organisms, any of which might be the origin of a given keratitis. The most commonly encountered organisms involved in microbial keratitis show tremendous geographic variance; some of the more commonly known infectious agents are shown in Table 113.1. Although the climate, vegetation, soil, and individual patient factors tend to favor specific organisms, any known organism can cause microbial keratitis, given the appropriate conditions and predisposing risk factors.

TABLE 113.1 Partial List of Causative Agents in Microbial Keratitis

Bacteria

Gram-Positive Cocci

Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae, Streptococcus pyogenes, viridans streptococci
Enterococcus faecalis
Peptostreptococcus spp.

Gram-Positive Bacilli

Bacillus coagulans, Bacillus cereus, Bacillus licheniformis
Brevibacillus (Bacillus) brevis, Brevibacillus (Bacillus) laterosporus
Corynebacterium diphtheriae
Clostridium perfringens, Clostridium tetani

Gram-Negative Coccobacilli

Neisseria gonorrhoeae
Moraxella lacunata, Moraxella nonliquefaciens, Moraxella catarrhalis
Acinetobacter calcoaceticus
Pasteurella multocida
Achromobacter xylosoxidans

Gram-Negative Bacilli

Pseudomonas aeruginosa, Pseudomonas stutzeri, Pseudomonas fluorescens
Burkholderia (Pseudomonas) mallei
Proteus mirabilis
Serratia marcescens
Escherichia coli
Klebsiella pneumoniae
Morganella morganii
Aeromonas hydrophila
Bartonella henselae

Mycobacteria

Mycobacterium tuberculosis, Mycobacterium chelonae, Mycobacterium gordonae, Mycobacterium mucogenicum

Actinomycetes

Nocardia spp.

Spirochetes

Treponema pallidum
Borrelia burgdorferi

Viruses

Herpes simplex virus
Varicella-zoster virus
Adenovirus
Vaccinia virus
Epstein-Barr virus
Rubeola
Enteroviruses
Coxsackievirus

Fungi

Fusarium spp.
Candida spp.
Aspergillus spp.
Acremonium spp.
Alternaria spp.
Penicillium spp.
Bipolaris spp.
Nosema spp.
Vittaforma (Nosema) corneae
Encephalitozoon spp.
Edenia gomezpompae
Exophiala phaeomuriformis

Chlamydia

Chlamydia trachomatis

Parasites

Acanthamoeba polyphaga, Acanthamoeba castellanii
Onchocerca volvulus
Leishmania brasiliensis
Trypanosoma spp.

Modified from O'Brien TP. Keratitis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. *5th ed. New York: Churchill Livingstone; 2000:1257–1266.*

Anatomic Protection

The epithelial surface, with its tight junctions formed by desmosomes and hemidesmosomes, is remarkably resistant to the host of virulent organisms found in the surrounding ocular environment. The tear film, containing antimicrobial enzymes, combined with the mechanical action of the blinking eyelids, reduces the likelihood of microbial attachment to and survival on the corneal surface. In general, microbial agents do not cause keratitis in immunocompetent hosts or those without prior epithelial injury. However, there are exceptions in which organisms such as *Neisseria gonorrhoeae, Listeria monocytogenes, Shigella,* and *Corynebacterium* spp. may invade an intact epithelial surface.

Geographic Variation

The prevalence of various kinds of microbial keratitis varies by US regions. Fungal keratitis is present more in the southern regions, whereas bacterial keratitis is more prevalent in the northern regions. Gram-negative bacteria are most prevalent in the southern regions when compared to northern locations.[10]

In other developing countries, such as South Africa, herpetic keratitis, complicated by bacterial superinfection, is the main kind of microbial keratitis.[11]

Risk Factors

Predisposing risk factors associated with microbial keratitis usually involve disruption of the corneal epithelium, such as by contact lens wear, trauma (surgical and nonsurgical), contaminated ocular medications, and altered structure of the corneal surface. Contributing risk factors include diabetes mellitus, systemic immunodeficiency, exposure keratopathy (e.g., Graves exophthalmopathy, Bell palsy), surface alteration from or with dysfunctional tear states (e.g., Sjögren syndrome, neurotrophic cornea, chemical burn, Stevens-Johnson syndrome, medication related), anatomic abnormalities (e.g., neoplasia, cicatricial pemphigoid, traumatic lid scarring), and keratoprosthesis implantation (Boston type I keratoprosthesis).[12]

Nonsurgical ocular trauma reportedly accounted for 48% to 65% of all corneal ulcers in some developing countries,[9,13] but such trauma was responsible for only 27% of corneal ulcers reported in 1987 at one large trauma referral center in the United States.[14] Trauma has also been the leading cause of microbial keratitis in pediatric populations.[15] In a more recent survey, potential predisposing risk factors were identified in 91% of 300 cases of suspected bacterial keratitis: 50% resulting from contact lens wear, 21% from ocular surface disease, 15% from nonsurgical trauma, and 4% from corneal surgery.[16]

Contact Lenses

Contact lenses remain the most common risk factor for microbial keratitis diagnosed in the United States. The incidence of microbial keratitis ranges from 0.4 to 5.2 per 10,000 person-years for rigid gas permeable and soft contact lenses to greater than 20 per 10,000 person-years for overnight contact lens use.[17] The reported percentage of contact lens–associated corneal ulceration in the general population has increased from 0% in the 1950s and 1960s to 31% in the 1970s and more than 50% of all cases since the 1980s.[7] In a 2010 study in Northern California, Jeng and coworkers[17a] reported a substantially higher rate of corneal ulcers in contact lens wearers, compared with non–contact lens wearers. They reported the incidence of corneal ulceration in contact lens wearers as 130.4 per 100,000 person-years, compared with non–contact lens wearers, who had an incidence of ulcerative keratitis of 14.0 per 100,000 person-years.[19a]

Since the 1990s, contact lens wear has accounted for 55% to 65% of diagnosed microbial keratitis cases,[4] where *Pseudomonas aeruginosa* is reported to be the predominantly isolated microbe from the corneal and contact lens cultures as well as contact lens case cultures.[18] Recent outbreaks of microbial keratitis in contact lens wearers have involved *Acanthamoeba* and *Fusarium* spp.,[19] which historically have been involved only rarely in cases of contact lens–associated microbial keratitis. An outbreak of *Acanthamoeba keratitis* was detected in the United States in 2007, where cases had been increasing since 2004.[19a] In the United States its reported incidence is low (0.15 per million), and in the United Kingdom it is more (1.4 per million). In terms of its incidence among all keratitis cases, *Acanthamoeba* keratitis is reported to account for 1% to 1.4% of all such microbial keratitis cases in countries with less common contact lens usage compared to 4% of all such cases in countries with more common contact lens usage.[20] These outbreaks may have been associated with the improper use of certain multipurpose contact lens solutions, with two multipurpose solutions having been identified as major contributing factors to the risk of microbial keratitis. The risk of microbial keratitis is reported to also increase because of greater microbial adherence to the lens, stemming from inadequate rinsing while also failing to rub the lenses properly as part of the cleaning process.[21]

Several explanations regarding pathology of contact lens–induced microbial keratitis have been proposed. Typically, in contact lens cases, bacteria multiply because they are protected from disinfection by bacterial biofilm. Evans and Fleiszig[22] proposed that in terms of contact lens–induced *P. aeruginosa* keratitis, biochemical changes of the corneal surface, due to tear fluid and bacterial trapping against the cornea under the lens, are the likely causes of microbial keratitis. In addition, bacterial adaptation to ocular surfaces increases the risk of microbial keratitis. Blockage in efficient tear exchange between tears above and tears under contact lens areas also can lead to an imbalance in homeostasis and a decrease in antimicrobial activity of the tears trapped under the lens.[23] Shin and associates[24] have reported that the baseline eye microbiome of contact lens wearers is different from those of nonwearers.

A study in Australia was performed to establish the risk factors for moderate and severe microbial keratitis among daily contact lens wearers. Independent risk factors for moderate and severe keratitis, while adjusting for age, gender, and lens material type, included poor storage case hygiene (odds ratio [OR], 6.4), infrequent storage case replacement (OR of 5.4), solution type (multipurpose solution A; OR, 7.2), occasional overnight lens use (<1 night/wk; OR, 6.5), high socioeconomic status (OR, 4.1), and smoking (OR, 3.7).[25]

With regard to preservation and antimicrobial solutions, Lin and coworkers[26] reported excellent anti–*Staphylococcus aureus* activity from preservatives with polyaminopropylbiguanide (PAPB), chlorhexidine, and the biguanide function group, and an excellent synergistic anti–*P. aeruginosa* activity (~7 times more potent than the drugs available today) from a combination of ethylenediaminetetraacetic acid (EDTA; 5000 ppm), PAPB (5 ppm), and chlorhexidine (30 ppm). Thus the proposed multipurpose solution containing a combination of PAPB, chlorhexidine, and EDTA could help decrease the incidence of contact lens–induced microbial keratitis.

It is worth noting that fluoroquinolones alone can be ineffective against contact lens–related keratitis. Thus empirical combined regimens should be considered as a more effective option.[27]

Contact lens use in conjunction with preexisting ocular surface conditions (such as blepharitis, corneal ulcer, Stevens-Johnson syndrome) is reported to be a significant risk factor for infectious keratitis development in pediatric populations.[28] *Acanthamoeba, Staphylococcus,* and *P. aeruginosa* are the most commonly isolated microorganisms for the infectious keratitis development.

Laboratory Data and Clinical Response

Clinicians often culture the contact lens and the contact lens case in addition to the patient's cornea despite imperfect sensitivity.[29,30] False-positives are too frequent to recommend this procedure. In one study, the significance of cultures from the lens or case could be confirmed by corneal cultures in only 25% of the cases.[31] Gram-negative organisms, such as *P. aeruginosa,* which can be cultured from the lens or case, are indeed associated with contact lens–induced microbial keratitis; however, gram-positive organisms, such as *Staphylococcus* and *Streptococcus* spp., have often been shown to be responsible for a majority of these ulcers even when gram-negative organisms have been recovered from the contact lens or storage case. Contact lens use alone can produce sterile inflammatory infiltrates that resolve spontaneously with discontinued use of the lens.

CLINICAL PRESENTATION

Eye Pain

Inflammation of the cornea, one of the most richly innervated tissues in the body, generally is accompanied by severe pain and significant discomfort, which can greatly affect the physical examination. The continued movement of the eyelids over a corneal lesion further adds to the patient's discomfort during examination. Judicious use of a topical anesthetic immediately preceding the eye examination is helpful. However, long-term use of topical anesthetics has been implicated in continued epithelial defects and melting of the corneal stroma. Therefore it has become a classical teaching that topical anesthetics should not be prescribed beyond the examination process.

Conjunctival Injection and Discharge

The rapid onset of pain is often accompanied by significant conjunctival injection, tearing, photophobia, blepharospasm, and decreased vision. Discharge, so often associated with conjunctivitis, is not usually present other than in some cases of purulent bacterial keratitis. There may be some differences in the presence or absence of injection and, to some degree, tearing and discharge based on the etiologic agent (i.e., viral and parasitic keratitis may have minimal discharge; fungal keratitis may have minimal injection in the early phases).

Corneal Infiltrates

Other than the injection of limbal vessels, the noninfected regions of the cornea are generally clear. Therefore corneal inflammation appears quite different than inflammation in most other tissues. The invading organisms initiate a reaction whereby inflammatory cells from the limbal vessels and tear film migrate into the cornea, reducing its transparency. The resultant inflammatory reaction at the sites of a microbial replication are called "infiltrates." It is important to note that in patients with limited ability to mount an immune reaction, the infiltrates may be small in size, or even nonexistent, despite continued microbial growth. In patients who are able to mount a normal immune reaction, the reduction in size of the infiltrate during the course of antimicrobial therapy may be an important indicator of response to therapy.

Epithelial Defect

The infiltrate often has an overlying epithelial defect because the infectious agent generally enters the cornea through an epithelial defect that can rapidly increase in size with the microbial replication. Epithelial defects can best be visualized using a cobalt blue light after the addition of fluorescein, which will pool in areas of punctate and ulcerative defects. Infections caused by slow-growing, fastidious organisms (i.e., *Mycobacterium,* anaerobic bacteria) may have an intact epithelial surface.

Stromal Suppuration

Microbial keratitis generally produces a sharply demarcated epithelial ulceration and suppurative stromal inflammation. There is substantial crossover in the presenting characteristics of various microbial agents. Bacterial organisms generally produce a clearly defined, local inflammation; fungal elements can have a more diffuse or multifocal infiltrate. A number of slow-growing, fastidious organisms may present without an ulcer or a suppurative infiltrate.

Corneal Edema

The loss of transparency is further affected by the corneal edema that is present in almost all cases of microbial keratitis. The corneal clarity is very specifically maintained through the ability of endothelial cells to maintain a stable level of dehydration. The influx of fluid that accompanies the inflammatory cells can overwhelm the endothelium's "pumping" capacity, resulting in varying degrees of corneal edema. This

fluid may coalesce under the epithelium, forming uncomfortable bullous elevations. The discomfort may increase if the bullae rupture.

Corneal Neovascularization

Neovascularization of the cornea is a common occurrence with chronic inflammation but can present early in the course of severe keratitis. The presence of neovascularization not only affects the severity of the host inflammatory reaction but also has long-term consequences. After resolution of the inflammation, the vessels may regress slightly to the point of no longer carrying blood but still remain as empty channels ("ghost vessels"). If the neovascularization does not regress, the vessels not only provide a route for recurrent inflammatory cells but also can directly affect visual acuity and greatly decrease the potential for successful corneal transplantation.

Intraocular Inflammatory Reaction

Intraocular inflammation is not uncommon with microbial keratitis, especially with some of the more virulent gram-negative bacteria. These signs, including cell/flare, hypopyon, synechiae, and glaucoma, are less common with early fungal, viral, and parasitic etiologies, but could present during the course of any case of keratitis. Early, subtle changes may be difficult to detect and are often described as protein ("flare") and leukocytes ("cells") in the anterior chamber on slit-lamp examination. Late changes or signs of more aggressive organisms may be seen in a collection of fibrin and inflammatory white blood cells layering in the inferior portion of the anterior chamber (hypopyon). Adhesive scarring of the pupillary margin (posterior synechiae) or of the peripheral iris (peripheral anterior synechiae) may lead to an irregular pupil or elevated intraocular pressure (glaucoma), which may necessitate urgent medical or surgical treatment. This intraocular inflammation is generally considered sterile unless infection has penetrated the Descemet membrane and entered the anterior chamber.

Stromal Melting (Keratolysis)

Loss of corneal tissue (keratolysis) is a major consequence of the inflammatory reaction seen in microbial keratitis. It is most common with bacterial keratitis. Keratolysis may lead to irregular astigmatism, corneal thinning, visually significant scar formation, and, in severe cases, corneal perforation.

LABORATORY EVALUATION

The rather small area of active infection and the need to avoid unnecessary scraping dictate patient cooperation. This may be accomplished through use of topical anesthetics (although this may reduce growth of recovered organisms) in patients old enough to cooperate and may necessitate general anesthesia in children. The small amount of specimen to be obtained from the cornea requires careful advance planning and consultation with the microbiology laboratory as to how the specimen should be obtained, transported, and processed.

Several studies have shown no statistical difference in organism recovery if using sterile surgical blades, blunt platinum spatulas, or calcium alginate swabs (often dipped in trypticase soy broth). Corneal biopsies may be necessary, especially when fungal infections or late stages of *Acanthamoeba* are suspected. (Earlier stages of *Acanthamoeba* have organisms in the more superficial layers.) Shave biopsies or partial thickness 1- to 2-mm trephined specimens may be possible at the slit lamp but are better performed in a minor operating room. Lamellar keratoplasty is not usually necessary, but in cases in which a rapidly progressive, necrotizing keratitis is refractory to treatment or identification is otherwise impossible, or both, a diagnostic and therapeutic penetrating keratoplasty (host corneal removal and transplant) may be necessary.

Stains and Media Inoculation

Material from the scrapings should be transferred directly to glass slides and appropriate culture media (see Chapter 16). The slides should be clean, to avoid artifacts, and sterile, to avoid contaminating the instrument. Multiple slides are desirable to permit Gram stain; calcofluor or other fungal stain; and acid-fast stain. *Chlamydia,* herpesviruses, mycobacteria, and *Acanthamoeba* require special methods for culture.

In addition to culturing the suspected cornea, it may be helpful to culture material from the eyelids, conjunctiva, ocular medication bottles, contact lenses, storage cases, and perhaps the uninvolved eye, to establish the flora uniquely associated with the patient. If the patient had been treated before evaluation and there is uncertainty as to the diagnosis, it may be wise to consider stopping the medication for 12 to 24 hours and then proceeding with culture. Obviously, antimicrobials should not be stopped in cases of severe or rapidly progressive ulceration.

Viral Cultures

Viral keratitis is unique among microbial keratitides in that the diagnosis is often possible based on morphology and patient history. Polymerase chain reaction for herpes simplex virus and herpes zoster virus is now readily accomplished in most routine diagnostic laboratories (see Chapter 16). Viral cultures are less sensitive than polymerase chain reaction but, if used, specimens for viral culture must be placed in transport media and inoculated into cell culture the same day.

BACTERIAL KERATITIS

Etiology

Bacterial keratitis is reported to be the cause of ulcerative keratitis in 80% of the patients worldwide.[32] It is associated mostly with contact lens use in the United States.[4] In the past, several published studies have reported that bacterial pathogens are responsible for 65% to 90% of all cases of microbial keratitis.[33,34] In one large survey, a microbial organism was isolated in 49% of 5845 cases of suspected infectious keratitis; 82% were bacterial, 16% fungal, and 2% parasitic.[35] A smaller survey isolated an organism in 68% of 300 eyes suspected of having bacterial keratitis; 83% were gram-positive, 17% gram-negative, and 2% polymicrobial.[11] The majority of all bacterial keratitis is caused by five major groups: *Staphylococcus* spp.; *Streptococcus* spp. (*Streptococcus pneumoniae,* groups A to G streptococci); other gram-positive organisms (*Bacillus* and *Cutibacterium* spp.); gram-negative organisms, such as *Pseudomonas, Haemophilus, Moraxella;* and the Enterobacteriaceae (*Proteus, Serratia, Klebsiella, Enterobacter, Citrobacter*). The prominence of certain organisms responsible for bacterial keratitis has been changing over many years. *Streptococcus pneumoniae* was the most common responsible agent in the past, but other gram-positives, opportunistic commensals, *Pseudomonas,* anaerobes, and protozoa are now increasingly being reported. With the advent of refractive surgery, especially laser-assisted in situ keratomileusis (LASIK), more unusual organisms, such as *Nocardia* and *Mycobacterium* spp., are causing keratitis. The apparent changes in causal organisms could be the result of numerous factors: improved isolation techniques, less frequent culturing as highly effective broad-spectrum single agents (i.e., fluoroquinolones) have been developed, increased use of topical corticosteroids (i.e., refractive and cataract surgery), increased population of systemically immunodeficient patients, and an expansion in the use of soft contact lenses, especially extended-wear and cosmetic lenses.[36,37] A study in Toronto reported on the shifting trends in bacterial keratitis over the course of 11 years.[38] A total of 1701 consecutive corneal scrapings were taken from January 1, 2000, through December 31, 2010. A significant decrease in the percentage of gram-positive microorganisms was observed over time. The sensitivity of gram-negative isolates to tested antimicrobials was greater than 97% response for all the reported antibiotics; this was not the case for gram-positive isolates, for which resistance to the antibiotics was more common. Methicillin-resistant organisms accounted for 29.1% of all gram-positive cultures. The authors concluded that the empirical use of vancomycin in the setting of severe suspected bacterial keratitis may be justified given the shifting trends.[38]

Pathogenesis

The corneal epithelium and the Bowman membrane underneath it limit penetration of many organisms into the corneal stroma unless the barrier is breached by trauma. The few organisms that appear to invade in the absence of trauma appear to adhere and elaborate proteolytic enzymes or toxins that lyse the tissue barrier. Migration of leukocytes from the vessels in the corneal limbus into the infected cornea add to tissue destruction.[39]

Geographic Variation

Gram-positive organisms, particularly *S. aureus,* continue to be the most common agents causing bacterial keratitis in most series. The order of prevalence in one series from New York City was *S. aureus, Moraxella, Pseudomonas,* and *S. pneumoniae.*[33] A different order, *S. aureus, S. pneumoniae, Pseudomonas,* and *Moraxella,* was seen in a similar series from London.[40] *Pseudomonas* and *Streptococcus* spp. are the most common bacterial pathogens isolated in previously healthy eyes in the southern United States.[34] Bacterial ulcers are more likely to be reported from centers in developed countries, whereas fungal infections are more likely to be reported from developing countries. This is because there are more agricultural workers in the developing countries who are at greater risk of trauma.[41] The highest proportion of bacterial corneal ulcers are reported in studies from Australia, North America, the Netherlands, and Singapore. *Pseudomonas* ulcers were reported in greater proportion from a study in Bangkok, whereas the greatest proportion of staphylococcal ulcers were reported from a study in Paraguay.[41]

Gram-Positive Bacteria

The strains of staphylococci invading the cornea, usually *S. aureus,* are often resident strains from the patient's own flora.[42,43] *Staphylococcus epidermidis* is not a common infectious agent, but this organism, along with *Streptococcus* spp., can cause keratitis in immunodeficient patients and may be associated with chronic dacryocystitis.[44] In these cases of *S. epidermidis* and *Streptococcus* keratitis, ulcers may appear similar to those with staphylococcal hypersensitivity keratitis, in which corneal inflammation is thought to be a result of toxins produced by the conjunctiva-based organism or a hypersensitivity reaction to some portion of the bacterial cell wall.

Gram-positive aerobic bacilli do not often cause keratitis in immunocompetent individuals.[45] *Corynebacterium diphtheriae* is one of the organisms reported to invade intact epithelial surfaces. *Bacillus cereus* is a gram-positive rod that can cause severe ulcerative keratitis, often after an injury involving a foreign body.[46] *Nocardia* and *Mycobacterium* spp. are increasingly implicated in bacterial keratitis after refractive surgery (i.e., LASIK).

Staphylococcus hypersensitivity reactions may actually be the most common cause of keratitis. Although it is related to the bacteria, the hypersensitivity is a reaction to some exotoxin or antigen rather than direct inoculation or infection. This condition may exist in hosts who may not have any increased bacterial load other than what is considered the normal commensural load in healthy individuals. The punctate epithelial defects, marginal stromal infiltrates, phlyctenules, and peripheral ulcerations are theorized to result from either type III or type IV hypersensitivity reactions. Histologic analysis reveals the presence of plasma cells and lymphocytes in the peripheral cornea but an absence of infectious organisms. Further support for the noninfectious etiology comes from the reduction in pathology when treated with topical steroids alone.

Lichtinger and coworkers[38] reviewed the distribution, current trends, and resistance patterns of bacterial keratitis in Toronto from January 1, 2000, through December 31, 2010. They identified a decreasing trend in gram-positive isolates. The most common isolate was coagulase-negative staphylococcus.[38] In another study, Shalchi and colleagues[48] reported a high level of gram-negative keratitis and highlighted a trend of increasing gram-negative infection in cultures isolated in the United Kingdom over a 10-year period.

Gram-Negative Bacteria

Pseudomonas aeruginosa is a particularly virulent and generally most common gram-negative organism implicated in bacterial keratitis.[38] Untreated *P. aeruginosa* keratitis progresses quite rapidly from suppuration to perforation, mainly because of swift corneal destruction from the associated proteolytic enzymes.[49,50] A characteristic inflammatory ring of neutrophilic infiltrate may surround the lesion.[51,52] This "ring infiltrate" is not unique to gram-negative organisms; it can also be seen in fungal, viral, and *Acanthamoeba* keratitis. Patients in burn units and intensive care settings often have altered mental status or anatomic injuries that make ocular exposure and corneal desiccation more common. When this is combined with the frequent colonization of such units with *P. aeruginosa,* this organism can be a significant cause of keratitis. *Pseudomonas aeruginosa* was identified as the most common gram-negative bacteria isolated in cultures performed on suspected bacterial keratitis from January 1, 2000 through December 31, 2010.[38]

Less common gram-negative entities have been reported to cause keratitis. Although *Morganella morganii* keratitis may be clinically indistinguishable from *P. aeruginosa* keratitis, *Delftia* (*Pseudomonas*) *acidovorans* and *Pseudomonas stutzeri* usually have a more benign course.[53] *Serratia marcescens* has been implicated in contact lens–associated keratitis.[54] *Moraxella* keratitis may be more common in alcoholics and less common in patients with chronic ocular surface disease.[55,56]

Although *N. gonorrhoeae* is more commonly associated with conjunctivitis, it can penetrate an intact corneal epithelium and cause keratitis. The rather explosive onset and copious purulent exudates may obscure a diagnosis of keratitis. The corneal infiltration may be secondary to the effects of the conjunctival infection. *Neisseria gonorrhoeae* can produce such marked infiltration and edema that the affected conjunctiva may protrude or drape over the corneal surface, exposing the epithelium to numerous proteolytic enzymes; ulceration can quickly result. *Acinetobacter* can produce a keratitis that is clinically indistinguishable from *Neisseria* and can appear morphologically similar on Gram stain.

Mycobacteria

Mycobacterium keratitis had been decreasing in prevalence, paralleling the reduction in systemic tuberculosis. Although primary tuberculous keratitis still is uncommon, an increase in systemic immunodeficient hosts as well as incisional refractive surgery (i.e., LASIK) has been accompanied by an increase in *Mycobacterium* keratitis (*M. fortuitum, M. chelonae, M. gordonae,* and *M. avium-intracellulare*).[57,58] Infection with atypical *Mycobacterium* spp. may be indolent with mild inflammation, therefore delaying the diagnosis.[59] Several cases of mycobacterial keratitis after LASIK have been reported in the literature. The most frequently involved pathogen is *M. chelonae* (66%).[59,60] These nontuberculous species can be quite difficult to isolate and eradicate because they follow a chronic indolent course and are often resistant to conventional antitubercular medications. In the case of refractive surgery, the location under the LASIK flap causes difficulty in obtaining cultures as well as direct application of topical medications. *Mycobacterium* spp. are responsible for eventually producing keratitis in about 15% of patients with tuberculoid leprosy but in nearly 100% of those with lepromatous leprosy.[61,62]

Therapy for Bacterial Keratitis

Immediate, Aggressive Therapy

Aggressive antimicrobial therapy is the primary approach with infectious keratitis. Topical administration is the most common route, and has become the classical approach to manage bacterial keratitis. Other treatment options include antibacterial therapy using subconjunctival injections and parenteral and oral routes. Additionally, antibiotic-soaked collagen shields/soft lenses have been, or are currently being, used. The clinician must decide whether to initiate immediate antimicrobial therapy, either directed or broad spectrum, or to wait for laboratory identification of the offending agent. If bacterial keratitis is suspected, the practitioner is advised to initiate therapy immediately after obtaining corneal specimens for microbial identification. The explosive nature of bacterial keratitis suggests the need for immediate therapy, perhaps guided by results of Gram or Giemsa stains, in all suspicious cases. The rather indolent course of fungal and *Acanthamoeba* keratitis and the significant commitment to months of costly treatment might allow a delay in therapy until a causative agent is identified. If severe suppurative keratitis is seen, the Gram stain and smear will guide the selection of medication. One specific medication may be selected if only one type of bacterium (gram-positive or gram-negative) can be positively identified and the patient has not previously started an antibiotic. If two or more types of bacteria are identified, if the stain and smears are equivocal, or if the patient has been on any type of antimicrobial agent, then broad-spectrum therapy is initiated.

Hospital Admission

An important decision in treating keratitis involves hospitalization or outpatient care. Hospitalization is rarely required, but it may be necessary

for noncompliant patients or for patients with rapid necrosis or thinning. The potential for a rapid downturn and possible corneal perforation should give the clinician a low threshold for admission. The high frequency of antimicrobial administration (perhaps hourly around the clock) and close monitoring may make outpatient care impractical, especially for those living alone, living far from the hospital or clinic, or otherwise unable to comply with such demands.

Antibiotic Solutions

The route of antibiotic administration should be based on the severity of the disease but often includes hourly (or more frequent) dosing, especially in cases of severe suppurative keratitis. Although patients may prefer ointments for ease of delivery and the comfort associated with the carrier, frequent administration of topical solutions is recommended because they can penetrate ocular tissues and achieve higher concentrations better than antibiotics in ointment formulations. Commercial pharmacies do not often provide concentrated (fortified) antibiotics, but compounding and hospital-based pharmacies can easily formulate fortified antibiotics using most parenteral antibiotic preparations.

Although bacterial ulcers typically respond to treatment with available topical antibiotics, a report by the CDC on the rise of rates of antibiotic-resistant infections, such as methicillin-resistant *S. aureus,* has led to huge concern.[62a] These ocular isolates are reported to be resistant to the most commonly prescribed antibiotic class, the fluoroquinolones.[63–65] The Steroids for Corneal Ulcer Trial (SCUT) identified correlations between in vitro susceptibility and clinical outcomes, which demands that corneal culture and sensitivity testing be performed for all corneal ulcers.[66–68] Response to treatment assessment is always critical.

Another concern is poor clinical outcomes resulting from irregular astigmatism and corneal opacity even when the bacterial ulcer pathogens are susceptible to topical antibiotics. The way to have strong impact on the clinical outcomes is by identifying the factors that resolve the inflammatory response to infection that results in corneal melting and scarring.[4]

Local and Systemic Administration

Subconjunctival injection of antibiotics had been more common in the past and is one way to attain a peak concentration without compliance issues. However, the discomfort and temporary nature make this less attractive, and frequent topical administration of fortified antibiotics can achieve adequate tissue levels. Parenteral administration is uncommon and generally used only in suppurative keratitis with impending or actual perforation or bacterial extension involving the sclera.

Contact Lenses and Collagen Shields

Antibiotics have been administered through the use of collagen shields and soft contact lenses.[69] Although these methods have been used experimentally, there are no controlled clinical studies detailing efficacy and safety. New technologic advances in polymer formation and microspheric packaging of antibiotics have allowed more practical ways to actually impregnate antimicrobials into the contact lens rather than simply soaking the lens or shield in the antibiotic as is done currently. Polymer inserts have been designed to theoretically increase the duration of the drug in the tear film. A rather simple strategy to include drug delivery to the corneal tissue involves placement of temporary punctal plugs to reduce the outflow from the ocular surface.

Further, because collagenases are involved in protein degradation and keratolysis, simply stabilizing corneal melting through anticollagenases such as tetracyclines may also reduce the incidence of severe complications of infectious keratitis, such as corneal perforation.[70–72] Studies involving tetracyclines, however, have only been either in vitro or in vivo studies. High-quality randomized controlled trials in humans are needed to guide clinicians in the use of adjuvant doxycycline for the treatment of corneal ulcers.[4]

Unique Pharmacokinetics With Topical Antibiotics

Although laboratory identification is quite helpful, the standard sensitivity testing has its limitations in treating ocular infections. The minimal inhibitory concentration (MIC) determinations performed in the laboratory are based on antibiotic concentrations that are achievable through the host's serum. The concentrations achievable through direct topical administration can be many thousands of times greater than that measured in the serum after parenteral administration. This might lead to an organism being labeled "resistant" to testing with an antibiotic at achievable serum concentrations, although it may well be in the process of eradication with that same drug through the highly concentrated topical approach. This highlights the clinical response as being the best indicator of actual susceptibility, not to the exclusion of laboratory sensitivities but within the unique limitations in dealing with the direct approach in eye conditions. Direct application to the infected area may avoid dealing with numerous issues critical in systemic therapy: distribution space, first-pass clearance, absorption characteristics, toxic reaction in nontarget tissues, and impact of renal or hepatic failure.

Initial Therapy

The ideal initial antimicrobial agent should be effective (bactericidal vs. bacteriostatic) against the common or suspected corneal pathogens and have low rates of resistance, minimal toxicity to ocular tissues, comfort on administration, and rapid penetration into the ocular tissues. Traditionally, broad-spectrum therapy for suspected bacterial keratitis has been the combination of a topical cephalosporin (or vancomycin) and an aminoglycoside (tobramycin or gentamicin), all as fortified concentrations. The main disadvantages of such treatment involve the ocular irritation, difficulty of obtaining noncommercially available solutions, significant cost, and continued refrigeration of some preparations. These inconveniences have led to an increasing interest in initial single-agent therapy by using fluoroquinolones. Whether as single agents or in combination, treatment generally begins with hourly dosing and then is tapered according to the clinical response. The fortified preparations are often continued for 10 to 14 days, after which a broad-spectrum nonfortified antibiotic may be given until resolution.

Many classes of antibiotics have been used for the treatment of specific classes of organisms, often based on Gram stain and eventual identification. The advent of the broad-spectrum fluoroquinolones has altered some of these traditional classes and treatment pathways, but many still hold true. Topical cephalosporin preparations are often used in gram-positive keratitis, especially with *Staphylococcus* spp. Vancomycin is an alternative if resistance is suspected. Gentamicin and tobramycin are the most common therapeutic choices in gram-negative keratitis. Drops are readily available commercially after the clinical improvement warrants a change from the fortified preparation.

Topical Fluoroquinolones

The development of fluoroquinolones has radically altered the previously standardized treatment of bacterial keratitis. Cultures were performed on all patients and all were generally started on combination fortified antibiotics. The efficacy of the fluoroquinolones, however, has made some consider monotherapy and question the need for culturing in all cases. The agents responsible for this shift were the second- and third-generation fluoroquinolones: ciprofloxacin, ofloxacin, and levofloxacin. Fourth-generation fluoroquinolone topical antibiotics (moxifloxacin, gatifloxacin) were introduced later to reduce the risk of bacterial resistance in view of the structural modifications and dual inhibition mechanisms of these antibiotics.[73] The spectrum of coverage at the high concentrations obtained locally is quite similar for the second- and third-generation fluoroquinolones, showing activity against most gram-negative aerobes and many gram-positive organisms.[74] These fluoroquinolones have significant activity against *P. aeruginosa,* including strains that may be resistant to other antimicrobials. *Haemophilus, Neisseria,* and *Moraxella* spp. are quite susceptible to any of the fluoroquinolones. Ciprofloxacin, ofloxacin, and levofloxacin have reasonable activity topically against some *Mycobacterium* and *Chlamydia* species. The greatest gap in coverage of second- and third-generation fluoroquinolones was with *Streptococcus* spp. and anaerobic bacteria.

The fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, inhibit bacterial DNA gyrase and topoisomerase IV, which results in increased antibiotic potency against gram-positive organisms and broad-spectrum activity against gram-negative bacteria.[75] Studies of the MICs of fourth-generation fluoroquinolones showed similar or better ability to kill causative bacteria in infectious corneal ulcer than

earlier-generation fluoroquinolones.[73,76,77] Fourth-generation fluoroquinolones have higher potencies against gram-positive organisms. However, ciprofloxacin is still better than the third- and fourth-generation fluoroquinolones against gram-negative bacteria, including *P. aeruginosa*.[78] Moxifloxacin has been reported to achieve the highest conjunctival, corneal, and aqueous concentrations.[73]

Comparison of Fluoroquinolones and Fortified Antibiotics

Any new medication or alteration in standard treatment protocols is best accepted after direct comparison with the gold standard. There are several comparative studies of the fluoroquinolones and the fortified combination therapies. In a randomized, masked comparative study of 122 patients, second-generation fluoroquinolones were found to be as efficacious as fortified gentamicin and fortified cefuroxime.[79] In another multicenter, randomized study, fluoroquinolones also compared favorably with fortified tobramycin and fortified cefazolin.[80] A similarly designed multicenter study involving 324 patients showed no difference using ciprofloxacin versus fortified cefazolin and fortified tobramycin.[81] In all three studies, the patients favored the fluoroquinolone, mainly for greater ocular comfort. The only adverse effect of the fluoroquinolones was the appearance of white crystalline precipitates near the epithelial defect in 16% of patients. This precipitate was seen more frequently with ciprofloxacin than with ofloxacin, consistent with a difference in the pH of the two agents. The precipitates can impair ability to monitor the subprecipitate infiltrates. The corneal precipitates appear to have no other clinical impact, and they resolve spontaneously after the medication is stopped.

Wong and coworkers[73] reviewed three clinical trials that investigated the clinical efficacy of the fourth-generation fluoroquinolones in treating infectious keratitis. The results of the three clinical trials correlate well with the results of the in vitro studies mentioned earlier, in that fourth-generation fluoroquinolones were comparable to fortified antibiotics and were better in the treatment of infectious keratitis.[82–84] The antibiotic resistance rates of bacterial isolates were consistently lower with moxifloxacin and gatifloxacin than almost all other antibiotics.[73] A large study was conducted by Constantinou and colleagues[82] that comprised 229 patients randomized to three treatment groups (moxifloxacin 1.0%, ofloxacin 0.3%, and the combined fortified tobramycin 1.33%/cefazolin 5.0%). Constantinou and colleagues reported that none of the bacterial isolates were resistant to moxifloxacin, 2.5% were resistant to ofloxacin, 14.8% to cefazolin, 1.6% to tobramycin, and 17.5% to chloramphenicol. Clinical outcomes (cure rate, mean time to cure, clinical sign score, and rate of serious complications) were not significantly different among the three groups.[82] Parmar and associates[83] compared the effect of topical gatifloxacin 0.3% with ciprofloxacin 0.3% for the treatment of patients with bacterial keratitis and ulcer size of at least 2 mm. These authors reported that culture results revealed a significantly larger proportion of gram-positive and gram-negative bacteria to be susceptible to gatifloxacin than to ciprofloxacin: 96.2% of gram-positive cocci were susceptible to gatifloxacin versus 60.4% to ciprofloxacin; all gram-positive bacilli were susceptible to gatifloxacin, but only 75% were susceptible to ciprofloxacin; and 92.9% of gram-negative bacilli were susceptible to gatifloxacin compared with 85.7% to ciprofloxacin. Even for *P. aeruginosa,* 87.5% were susceptible to gatifloxacin, whereas only 75% were susceptible to ciprofloxacin. With patients on gatifloxacin, 95.1% showed good response and complete healing of ulcer compared with 80.9% of patients on ciprofloxacin.[83] The third study, by Shah and coworkers,[84] compared the clinical effects of moxifloxacin 0.5%, gatifloxacin 0.5%, and combined fortified tobramycin 1.3%/cefazolin 5% on bacterial keratitis. All patients had ulcer size between 2 and 8 mm. These authors reported that all bacteria isolated were susceptible to the two fourth-generation fluoroquinolones. The cure rate of the fortified antibiotics group was 90%, and that of the gatifloxacin and moxifloxacin group was 95%.[84]

In contrast to these three clinical trials, a retrospective study in the United Kingdom by Shalchi and colleagues[48] determined the scale of antibiotic resistance in microbial keratitis. They reported no trend in increasing resistance of ciprofloxacin and advised against a change to fourth-generation compounds.[48] Wong and coworkers[73] attributed this discrepancy to the different spectrum of pathogens in bacterial keratitis, with 38.9% gram-positive and 61.1% gram-negative in the UK study. Fourth-generation fluoroquinolones are known to have higher potency against gram-positive pathogens and lower potency than second-generation fluoroquinolones in the inhibition of *P. aeruginosa.* Of note is that *P. aeruginosa* only constituted 7% of all the isolates in the Constantinou study compared with 49.1% in the United Kingdom.

A Cochrane-style review of high-quality, randomized, controlled clinical trials on the management of bacterial keratitis with topical antibiotics found no significant difference in the relative risk of treatment success (defined as complete reepithelialization of the cornea) or in the time to cure, when comparing two or more topical antibiotics over at least 7 days. This review included 16 trials.[85] The aminoglycoside-cephalosporin combination reportedly caused an increase in the relative risk of minor adverse events such as chemical conjunctivitis and ocular discomfort compared to fluoroquinolones; however, it did not increase risk of major complications.[80–82,85]

In summary, fourth-generation fluoroquinolones are reasonable monotherapeutic alternatives to the combination of fortified antibiotics in the management of infectious keratitis. Further studies are needed to compare the response of *P. aeruginosa* infections to these antibiotics before concluding that fluoroquinolones are as effective as the standard combination of fortified antibiotics in the management of infectious keratitis.[73]

Proposed Therapy Guidelines

The spectrum, safety, comfort, cost, and availability of the fluoroquinolones make them a very appealing choice in treating keratitis. Although many practitioners use these medications as first-line agents, fluoroquinolones are still not recommended as empirical therapy in vision-threatening keratitis. Initial treatment, often with combination agents directed toward the likely pathogens, guided by laboratory evaluation, is still essential for such cases. General guidelines for managing keratitis are as follows; the best approach for corneal ulcers is still not definite.

1. Corneal scrapings are indicated in patients with suspected infectious keratitis when risk factors are present, when there is a large central infiltrate, or after empirical therapy has failed.
2. Culture should be done in all cases of suspected infectious keratitis in community- and hospital-based practices.
3. Fortified cefazolin and aminoglycoside should be used for more severe keratitis.
4. Monotherapy with a fourth-generation fluoroquinolone can be used for mild keratitis.

Topical Corticosteroids

The use of topical corticosteroids to decrease long-term sequelae of bacterial keratitis is controversial. An intense suppurative inflammatory reaction consisting mainly of polymorphonuclear leukocytes is induced by many bacteria responsible for keratitis. These neutrophils may destroy a significant amount of tissue through free radicals and the liberation of collagenases and gelatinases that dissolve the stroma. The rationale for corticosteroids is to prevent such tissue destruction and to improve outcomes by reducing scarring, neovascularization, and stromal melt.[86–89] Several studies have shown that concomitant use of topical steroids does not alter or reduce the bactericidal effect of antimicrobials.[90] In one study, Henry and associates[91] reported that patients using topical corticosteroids are at a higher risk of progression from keratitis to endophthalmitis; some others have reported delayed epithelial healing and worsening of infection.[92–95] A subgroup analysis of a randomized placebo-controlled study of topical steroids found that addition of corticosteroids within 2 to 3 days of initiation of topical antibiotics improved 3-month visual acuity.[96] On the other hand, a recent Cochrane review of adjuvant topical steroids for bacterial keratitis involving four randomized controlled trials found no difference in healing times or visual acuity outcomes between the topical antibiotics alone versus topical antibiotics in conjunction with topical steroids.[97–100] There is a concern that steroid use may promote a relapse of an organism that appeared to be clinically resolved but still had a low number of active bacteria. This may be the case with virulent

organisms that are difficult to eradicate and require only a low inoculum to establish an infection, as seen in some gram-negative bacteria such as *P. aeruginosa*.

Supportive Measures

Supportive measures in managing infectious keratitis are numerous. Topical cycloplegics can reduce the discomfort of ciliary spasm, reducing the associated photophobia and preventing synechiae (scarring/adhesions) of the pupil. If corneal ulceration is quite significant, a temporary soft contact lens may act as a bandage to relieve some of the discomfort while allowing repair of the stromal and epithelial surfaces without mechanical disruption from the eyelid. The contact lens itself can serve as a nidus for infection, but this should not be the case with the temporary placement of the contact lens combined with continued application of antibiotics. The change to commercial-strength antimicrobials is warranted as soon as clinically reasonable because the fortified antibiotics are epitheliotoxic and decrease epithelial healing.

Price and coworkers[101] have investigated the role of collagen cross-linking adjuvant therapy for microbial keratitis in 48 patients (confirmed bacterial etiology in 24 eyes, fungal in 7, and protozoan in 2). Despite encouraging results for superficial infiltrates, the potential benefit of this approach remains of limited value.

CHLAMYDIAL AND SYPHILITIC KERATITIS

Chlamydial Keratitis

Chlamydiae are small intracellular organisms dependent on their host cell for replication and prolonged survival.[102] Their unique multiphasic life cycle permits the pathogen to establish persistent infections, allowing the organism to escape immune clearance yet express virulence determinants that cause chronic inflammation.[103] In addition, long-lasting protective immunity does not develop after chlamydial infection, and reinfections are common.

Ocular Associations With *Chlamydia*

Chlamydiae cause a spectrum of acute and chronic ocular diseases, ranging from self-limited follicular conjunctivitis to trachoma, often with blinding sequelae.[104] Several serotypes of *Chlamydia trachomatis* can cause a follicular conjunctivitis known as adult inclusion conjunctivitis. The same serotypes can lead to neonatal conjunctivitis if an infected mother transmits the pathogen to the newborn during vaginal delivery. Repeated infections with certain serotypes can cause trachoma, a chronic follicular keratoconjunctivitis that remains the most common cause of preventable blindness in the world. In developed countries, sexually transmitted *C. trachomatis* rarely causes the sequelae of true trachoma, which is generally marked by repeat infection and chronicity.

The cicatricial phase of trachoma causes lid irregularities, leading to exposure or direct trauma from in-turned eyelids or eyelashes, which leads to corneal ulceration and opaque scarring, often long after resolution of the infective phase. The resultant effects on the cornea may predispose to bacterial superinfection, further adding to the disease morbidity.

Syphilitic Keratitis (Interstitial Keratitis)

The keratitis associated with syphilis, sometimes termed *interstitial keratitis* (IK), is not often seen in the active phase but is noted in subsequent examinations. The two major categories of IK are associated with syphilis and *Mycobacterium tuberculosis*. IK is rarely associated with acquired primary or secondary syphilis (<3% of all cases), with more than 90% caused by congenital syphilis. IK usually does not develop until the later phases of congenital syphilis, occurring in about 50% of all untreated patients. The typical presentation is during the early teen years; however, it can develop any time during the first two decades of life. Pain, photophobia, increased tearing, blepharospasm, and decreased vision are common during the acute phase. A severe iridocyclitis is present as the cornea becomes hazy, with significant reduction in vision over a few days. Neovascularization progresses centrally over the next months until the vessels coalesce in the central cornea, at which time there is a dramatic change in the disease process. After resolution of the corneal infiltrates and significant regression of the blood vessels (leaving empty channels or "ghost vessels"), some patients have a surprisingly significant return of visual acuity. Only about 10% have less than 20/200 vision; approximately 70% have between 20/20 and 20/100 vision. Lyme disease has also been implicated as a possible etiology in corneal disease, with *Borrelia burgdorferi* causing an IK similar to that seen with syphilis.[105]

Therapy for Chlamydial and Syphilitic Keratitis

Keratitis in patients with trachoma is largely due to the lid scarring or exposure resulting from the conjunctival disease and therefore requires treatment of the associated conditions to reduce the subsequent keratitis. Several generalizations can be made when treating other chlamydial eye infections. First, systemic rather than local therapy is necessary when treating adult inclusion conjunctivitis because the infected individual may harbor the pathogen in the genital tract. Similarly, newborns presenting with neonatal chlamydial conjunctivitis may harbor the organism in the lower respiratory tract and may need to be treated systemically. Individuals treated systemically do not need to be treated locally. Second, all sexual partners must be treated along with the infected patient to prevent primary infection in the partner as well as reinfection in the symptomatic individual. Third, repeat treatment may be necessary because clinical cure rates can be modest, especially for treatment of chronic chlamydial infection. Finally, antibiotics that achieve sustained tissue levels, high intracellular penetration, and low microbial resistance and require an infrequent dosing regimen are generally preferred. To this end, azithromycin is rapidly becoming the mainstay of therapy for many chlamydial infections, including *C. trachomatis*.

Therapy for Interstitial Keratitis (Syphilitic and Lyme Associated)

Syphilitic IK is an immune phenomenon that may benefit from topical corticosteroids, but antitreponemal therapy has little impact on the corneal process. However, such therapy may be necessary for other systemic manifestations of the disease and does seem to reduce the recurrence rate and likelihood of bilateral involvement. Lyme keratitis may be addressed through the use of corticosteroids, with systemic evaluation and treatment similar to that for syphilis.

VIRAL KERATITIS

Herpes Simplex Virus

Ocular herpes may be classified into three general groups: congenital and neonatal, primary, and recurrent. The global incidence of herpes simplex virus (HSV) keratitis has roughly been estimated to be 1.5 million, including 40,000 new cases of severe monocular visual impairment or blindness each year.[106] The combined incidence of epithelial and stromal keratitis in the United States has been estimated to be 18.2 per 100,000 person-years.[106] The vast majority of all ocular herpes infections are caused by HSV type 1 (HSV-1). Because infection is acquired by passage through an infected birth canal, 80% of neonatal cases are caused by HSV type 2 (HSV-2).[107,108] Multiple recurrences are far more common with genital and oral herpes than with ocular herpes. Studies have shown an 89% recurrence rate for genital and a 42% recurrence rate for oral HSV over a 1-year period. In contrast, the ocular herpes recurrence rate was 40% over a 5-year period, which is fortunate considering the visual consequences.[109,110] Epithelial ulcers ultimately respond to antiviral therapy, but stromal involvement may not readily clear, leaving a nebulous scar. In the absence of superinfection, the skin lesions heal without scarring.

Evidence has suggested that HSV-1 infection disrupts the normal equilibrium between angiogenic and antiangiogenic stimuli, leading to vascularization. Thrombospondins 1 and 2, matricellular proteins involved in wound healing, are potent antiangiogenic factors and appear to be one of the key players. Elucidating their roles in corneal scarring and vascularization may lead to improved therapies for herpes simplex keratitis.[111]

Ocular infection with HSV-1 continues to be a serious clinical problem despite the availability of effective antivirals. A 2008 review reported that despite intensive antiviral and antiinflammatory therapy, a significant percentage of patients do not respond to chemotherapy for herpetic

necrotizing stromal keratitis. Therefore the development of therapies that would reduce asymptomatic viral shedding and lower the risks of recurrent disease and transmission of the virus is crucial to decreasing the morbidity of ocular herpetic disease.[112]

Primary Herpes Simplex Virus Keratitis

Sixty percent of children are infected with HSV by age 5 years, all of whom then carry latent virus in their dorsal root ganglia.[113,114] Ocular disease resulting from primary infection or reactivation in the trigeminal ganglion may manifest in many forms, one of which is keratoconjunctivitis. In the absence of skin vesiculation, differentiation from adenoviral infection is aided by a careful search of the lid margins for signs of herpetic blistering.

Primary HSV keratitis is often atypical. Initially, there may be just a nonspecific diffuse punctate keratitis that evolves into multiple scattered microdendritic figures. There may be wandering linear serpiginous ulcers across the entire corneal surface.[109] The diffuse nature of this primary epithelial involvement is probably a function of the host's nonimmune state, which allows more widespread ulceration. Primary disease is, as a rule, confined to the epithelium in terms of clinical findings. Stromal involvement is not usually seen in this phase of the disease, presumably because the host is not immunologically programmed against the virus. Primary ocular herpes should not be confused with "first ocular occurrence." The former is a first encounter with the virus; the latter is the first eye involvement with HSV in a patient who has had a subclinical oral or nasal infection and is immune. First ocular occurrence is therefore similar to recurrent ocular herpes as described next.

Recurrent Keratitis

Patients with recurrent ocular herpes have both cellular and humoral immunity against the virus. Herpes simplex–induced eruptions of the corneal epithelium are characteristically thin, branching dendritic ulcers; wider, branching dendrogeographic ulcers; or map-shaped geographic lesions, all caused by live virus. Little inflammatory cell reaction—polymorphonuclear leukocytes but no lymphocytes—is seen in this form of ocular herpes, but many free viruses lie in intracellular and extracellular locations, particularly in the basal epithelium.[115] Signs and symptoms include tearing, irritation, photophobia, and often blurring of vision. Because the only presenting clinical finding may be a watery conjunctivitis, the patient should be asked about any trauma, previous corneal ulcers, inflammation inside the eye (iritis), nasal or oral cold sore, genital sores, recent use of topical or systemic steroid or immunosuppressive drugs, and immunologic deficiency states, malignancy, organ transplants, or chronic eczema. If corneal examination reveals dendritic or even geographic ulceration, the infectious agent is HSV until proven otherwise. In HSV keratitis, corneal sensation is reduced in about 70% of patients,[116] although it is almost never totally absent as often seen in varicella-zoster keratitis. The more marked the stromal scarring, found in more chronic cases, the more marked is the decrease in sensitivity. The corneal lesions begin as a fine, transient, punctate keratitis that coalesces to form dendritic, dendrogeographic, or geographic ulcers. In an eye that has had many recurrences or is receiving steroids without antiviral prophylaxis, the more subtle stages may be bypassed, and the cornea may simply break down in rapidly forming geographic ulceration. The actual incidence of infectious epithelial HSV keratitis in immunocompetent patients may be much higher than suspected clinically. Kodama and colleagues[116] reported that of 48 eyes with diagnoses of nonherpetic conditions, 19 were culture positive for HSV. Contrary to common opinion, recurrent epithelial infections are not always due to the patient's original HSV strain. Remeijer and associates[117] reported a study on 30 patients in whom sequential corneal HSV-1 isolates revealed that 63% were genotypically the same from recurrence to recurrence, whereas 37% were actually genetically different.

Stromal Inflammation and Intraocular Reaction

Stromal reaction is usually absent or mild and confined to the anterior layers in milder epithelial infections. On occasion, however, even mild epithelial infection may be associated with notable stromal edema and iritis. These eyes are more likely to go on to chronic recurrent immune disease and scarring, resulting in visual loss. Concurrent or future stromal disease may be minimized, as well as healing rate enhanced, by gentle débridement of the infected epithelium with a sterile cotton-tipped applicator before instituting antiviral chemotherapy.[118,119] Such débridement is thought to remove much of the immune-inciting antigen that could penetrate to deep stromal layers.

Neurotrophic Keratitis

On occasion, despite adequate antiviral therapy, epithelial ulcers do not completely heal or, having healed, break down again in an ovoid or dendritiform pattern. This is trophic, or "metaherpetic," keratopathy. Clinically, a trophic ulcer may be distinguished from an actively infected viral ulcer by the appearance of its edge. Trophic ulcers have gray, thickened borders formed by heaped-up epithelium unable to move across or adhere to the damaged ulcer base. In contrast, actively infected ulcers have discrete flat edges that may change their configuration as the ulcer erodes newly infected epithelium. Persistence of trophic ulceration over several weeks or months poses a threat to the integrity of the globe. The longer the ulcer is present, the greater is the chance of collagenolytic activity, with subsequent stromal melting (thinning) down to the Descemet membrane and perforation.

Treatment is aimed at protecting the corneal surface and damaged basement membrane because of the neurochemical and mechanical nature of the problem. Therapeutic approaches include treatment of any meibomian gland dysfunction; copious lubrication with unpreserved artificial tears, gels, or ointments, or a combination of these; lateral tarsorrhaphy; therapeutic soft contact lenses; tetracyclines; suppression of inflammation; prophylactic oral antiviral agents; autologous serum drops; and amniotic membrane transplant or, on occasion, conjunctival transplant, conjunctival flap, penetrating keratoplasty, or keratoprosthesis.[120] It has been reported that neurotrophic corneal ulcer occurred after a retrobulbar injection of chlorpromazine. The authors postulated that chlorpromazine may lead to sensory denervation to the cornea, with subsequent development of neurotrophic keratopathy, and they advise caution against this potential adverse side effect through proper patient safety, education, and postinjection management.[121]

Varicella-Zoster Virus

Contact with the varicella virus in the United States was formerly almost invariable,[122] but the use of varicella-zoster virus (VZV) vaccine as part of the recommended childhood immunizations has substantially reduced the frequency of chickenpox. Ocular involvement in chickenpox is diagnosed on the basis of an acute or recent history of chickenpox with ocular or periocular involvement with the vesicle-pustules.

VZV infection may involve small phlyctenule-like lesions that may erupt most commonly at the corneal limbus.[109,123,124] It is unclear whether these are due to live virus or to an immune phlyctenule-like reaction, or both. The cornea may develop superficial punctate keratitis: wispy, branching dendritic ulcers without terminal knobs (herpes simplex ulcers have knob-shaped endings on their branches).[125,126] Months after the acute disease, a disciform keratitis similar to that seen in HSV disease may develop.[127] This disciform reaction is steroid responsive but may recur and cause scarring similar to HSV keratitis. Less frequently reported varicella findings in the eye include dendritic keratitis and neurotrophic ulceration with corneal melting.

Herpes Zoster Ophthalmicus

Herpes zoster is a reactivation of infection with VZV. Approximately 50% to 72% of patients with periocular zoster have involvement of the ocular structures, develop chronic disease, and possibly suffer a moderate to severe degree of visual loss.[128] Of the three divisions of the fifth (trigeminal) cranial nerve, the first (ophthalmic) is by far the most frequently affected. Herpes zoster ophthalmicus (HZO) occasionally affects the maxillary division but rarely affects the mandibular division.[129] The first division of the fifth nerve, along with sympathetic branches from the ciliary ganglion, innervate the eyelids, forehead, and tip of the nose and the majority of the orbit and ocular adnexa.[130]

Clinical Manifestations of Herpes Zoster Ophthalmicus

In Liesegang's study of 94 patients with HZO, two-thirds had corneal involvement.[130] This took the form of punctate keratitis (51%), pseudodendrites (51%), anterior stromal infiltrates (41%), sclerokeratitis (1%), keratouveitis-endotheliitis (34%), peripheral ulcerative keratitis (7%), delayed mucous plaques (13%), disciform keratitis (10%), neurotrophic keratitis (25%), and exposure keratitis (11%). A delayed limbal vasculitis with or without anterior ischemic necrosis was also noted on rare occasions. Corneal disease may precede, accompany, or follow the acute disease by months to years and may recur in any of its many forms. The acute epithelial disease is considered infectious and may present as a diffuse superficial punctate keratitis or more commonly as migratory dendritic lesions that at first could be confused with herpes simplex. Piebenga and Laibson[131] also described herpes zoster dendrites that were culture negative but appeared as heaped-up, superficial plaquelike lesions, coarser than herpes simplex dendrites but lacking terminal bulbs (an important differentiating point), and staining poorly with fluorescein. These dendrites cause a foreign body sensation and are elevated, coarse, gray-white, swollen epithelial cells piled in plaques or a dendritiform shape on the corneal surface. They are both migratory and transitory and are usually associated with a neurotrophic keratitis (75%) or previous corneal inflammation (100%). Immune keratitis similar in appearance to HSV stromal disciform edema/endotheliitis may occur any time after the acute illness, most commonly first appearing after 3 to 4 months.

Corneal Anesthesia

Corneal sensation may be markedly diminished in even the mildest cases of clinically manifest herpes zoster keratitis. Sixty percent of patients have moderate-to-complete corneal anesthesia (neuroparalysis) secondary to the destructive VZV ganglionitis and to aqueous tear deficiency resulting from loss of the nasolacrimal reflex.[129,132,133] Anesthetic epithelial breakdown comprises one of the most dangerous aspects of herpes zoster keratitis. One-quarter of all HZO patients develop clinical signs of neurotrophic keratitis because of permanent corneal anesthesia. As the corneal epithelium becomes progressively unhealthier, oval epithelial defects may develop in the palpebral fissure or lower corneal area, with subsequent melting and corneal thinning. Neovascularization in these cases is a good sign and should be allowed to take place because healing often accompanies the process. Because many of these eyes are poor surgical risks, it is unlikely that a corneal graft would be successful.

Ocular Complications With Vaccinia (Smallpox) Vaccination

Recent attention to the development and use of a smallpox vaccine has brought about an interest in vaccinia keratitis; the vaccine directed against smallpox is derived from the bovine equivalent, vaccinia.[134] A study by Ruben and Lane[135] indicated that not only were the ocular complications of vaccination infrequent; they were also not notably vision threatening. Corneal involvement after autoinoculation is uncommon, with reports of approximately 1.2 cases per million primary vaccinations.[136] Other studies indicate postvaccinial keratitis in 6% to 37% of vaccinia cases with ocular involvement.[137,138] Keratitis appears more frequently in primary vaccinees than in revaccinees, which is probably a reflection of the immune status of the previously vaccinated patient. Long-term sequelae, such as madarosis (eyelash loss), punctal stenosis, and cicatricial lid changes are more common in cases with corneal manifestations (18%) than in ocular vaccinia without keratitis (2%). However, reexamination of patients with corneal vaccinia after 5 years revealed either no ocular residua or only minor corneal changes, including mild corneal scarring, ghost vessels, and subepithelial opacity with chronic conjunctivitis.[135]

Vaccinia Keratitis

Corneal manifestations of ocular vaccinia range from mild superficial punctate keratitis to interstitial or stromal keratitis, to disciform keratitis with keratic precipitates, to necrosis with perforation. As with epithelial herpes simplex or varicella-zoster keratitis, corneal epithelial vaccinia lesions stain with rose bengal early in the course of the disease and with fluorescein as an epithelial defect evolves. Direct infection of the corneal epithelium with vaccinia may present as multiple punctate lesions, as dendritiform lesions, or in a geographic pattern. All forms of vaccinia epithelial keratitis may closely resemble that seen with herpes simplex. Stromal keratitis caused by vaccinia may initially appear as scattered subepithelial opacities similar to those seen in epidemic keratoconjunctivitis. This pattern may evolve to ring infiltrates, ulceration, or stromal necrosis or scarring, which must be differentiated from *Acanthamoeba,* herpes zoster, and herpes simplex stromal keratitis.

Adenoviral Keratitis

Epidemic keratoconjunctivitis (EKC), caused by various adenovirus serotypes, is a highly contagious condition that can have explosive spread in schools, workplaces, and physicians' offices. The keratitis may have an early epithelial component, followed by a later subepithelial stage. Active viral replication within epithelial cells marks the early keratitis. The later-developing subepithelial infiltrates (SEIs) probably represent an immune response to viral antigens because microscopic analysis of SEIs reveals lymphocytes, degenerated collagen fibrils, and scarring, but no virus particles. A watery discharge, photophobia, and foreign body sensation are often accompanied by a hemorrhagic conjunctivitis with membrane formation. The keratitis progresses through a fairly orderly process of superficial epithelial keratitis, deep epithelial keratitis, and eventual SEIs.

Differential Diagnosis of Epidemic Keratoconjunctivitis

Pharyngoconjunctival fever is caused by different serotypes of adenovirus with a similar course of conjunctivitis but less commonly leads to epithelial keratitis and SEIs. Pharyngoconjunctival fever may begin in one eye but usually involves both eyes eventually. Enterovirus, molluscum contagiosum, Epstein-Barr virus, and coxsackievirus can be associated with a mild epithelial keratitis similar to the early stages of EKC. Keratitis associated with hemorrhagic conjunctivitis caused by enterovirus 70 is discussed in Chapter 112. Keratitis associated with measles (rubeola) generally is similar to that seen in EKC; however, in patients with significant malnutrition and vitamin A deficiency, measles keratitis can become a blinding disease with secondary bacterial infection and possible perforation of the globe.

Therapy for Viral Keratitis

Self-Limited Cases

Many of the cases associated with viral keratitis may not require specific antimicrobial therapy. There may be a twofold reason for this. First, a number of viral conditions are self-limited with relatively minor deleterious effects on the cornea, and second, the research and production of antiviral agents have not led to many viable treatment options, especially compared with those for bacterial keratitis. However, there are viral organisms that can cause significant visual or ocular morbidity, particularly when combined with the associated inflammatory response.

Therapy for Herpes Simplex Virus and Varicella-Zoster Virus

The management plans for both herpes simplex and herpes zoster have undergone many changes as more antiviral agents and information from basic research and clinical trials have become available. Tables 113.2 to 113.4 give the currently recommended treatments. Although topical acyclovir is just as effective as trifluridine with less ocular toxicity and is the first-line treatment for HSV keratitis in Europe, it is currently unavailable in the United States.[4,139] Acyclovir in oral form has also been shown to be effective against VZV keratitis, although the Herpetic Eye Disease Study (HEDS) I, a randomized controlled trial, found no significant improvement in the best spectacle-corrected visual acuity (BSCVA) when treating HSV stromal keratitis with oral acylovir.[4,140] On the other hand, HEDS II found that ocular HSV recurrence was 45% lower in the acyclovir group compared to the placebo group. HEDS II was a large, multicenter, randomized, placebo-controlled trial that evaluated the prolonged use of oral acyclovir for recurrent ocular HSV. The acyclovir group was reported to experience a 19% recurrence rate while the placebo group experienced a 32% recurrence rate ($P < .001$).[4,141]