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194 Chlamydial Infections

urogenital tract. The vagina yields the largest number of organisms; next most densely colonized are the periurethral area and the cervix. Ureaplasmas are isolated less often from urine than from the cervix, but M. hominis is found with approximately the same frequency at these two sites. Ureaplasmas are isolated from the vagina of 40–80% of sexually active, asymptomatic women and M. hominis from 21–70%. The two microorganisms are found concurrently in 31–60% of women. In men, colonization with each organism is less prevalent. A large U.S. prospective multicenter study of a nucleic acid amplification test for M. genitalium including male and female patients seeking care in diverse geographic regions found overall prevalence to be 10.3%. Mycoplasmas have been isolated from urine, semen, and the distal urethra of asymptomatic men. ■ ■CLINICAL MANIFESTATIONS Urethritis, Pyelonephritis, and Urinary Calculi In many episodes of Chlamydia-negative nongonococcal urethritis, ureaplasmas may be the causative agent. These organisms may also cause chronic voiding symptoms in women. The common presence of ureaplasmas in the urethra of asymptomatic men may suggest either that only certain serovars are pathogenic or that predisposing factors, such as lack of immunity, must exist in persons who develop symptomatic infection. Alternatively, disease may develop only upon initial exposure to urea plasmas. Ureaplasmas have been implicated in epididymitis. M. geni talium also appears to cause urethritis. M. genitalium and ureaplasmas do not have a known role in prostatitis. M. hominis does not appear to play a primary etiologic role in urethritis, epididymitis, or prostatitis. Evidence suggests that M. hominis causes up to 5% of cases of acute pyelonephritis. Ureaplasmas have not been associated with this disease. Ureaplasmas play a limited role in the production of urinary calculi. The frequency with which ureaplasmas reach the kidney, the predis posing factors that allow them to do so, and the relative frequency of urinary tract calculi induced by this organism (compared with other organisms) are not known. Pelvic Inflammatory Disease M. hominis can cause pelvic inflammatory disease. In most episodes, M. hominis occurs as part of a polymicrobial infection, but the organism may play an independent role in a limited number of cases. Data also support an association of M. genitalium with pelvic inflammatory disease. Ureaplasmas are not thought to cause pelvic inflammatory disease. Postpartum and Postabortal Infection Studies implicate

M. hominis as the primary pathogen in ~5–10% of women who have post partum or postabortal fever; ureaplasmas have been implicated to a lesser degree. These infections are generally self-limited; however, if symptoms persist, specific antimicrobial therapy should be given. Ureaplasmas also appear to play a role in occasional postcesarean wound infections. Nonurogenital Infection In rare instances, M. hominis causes nonurogenital infections, such as brain abscess, wound infection,

poststernotomy mediastinitis, endocarditis, and neonatal meningitis. These infections are most common among immunocompromised and hypogammaglobulinemic patients. Ureaplasmas and M. hominis can cause septic arthritis in immunodeficient patients. Ureaplasmas probably cause neonatal pneumonitis; their possible causal role in the development of bronchopulmonary dysplasia—the chronic lung disease of premature infants—has been extensively investigated, with most studies indicating at least a significant association. It is unclear whether ureaplasmas and M. hominis cause infertility, spontaneous abortion, premature labor, low birth weight, or chorioamnionitis. ■ ■DIAGNOSIS Culture and PCR are both appropriate methods for the isolation of urogenital mycoplasmas. Culture of these organisms, however, requires special techniques and media that generally are available only at larger medical centers and reference laboratories. Serologic testing is not recommended for the clinical diagnosis of urogenital Mycoplasma infections. Antibiotic resistance testing to guide appropriate therapy is becoming more available to clinical practice.

TREATMENT Urogenital Mycoplasma Infections Because colonization with urogenital mycoplasmas is common, it appears at present that their isolation from the urogenital tract in the absence of disease generally does not warrant treatment. Patients with recurrent urethritis or cervicitis after treatment failure of appropriate antibiotic therapy for sexually transmitted infections should receive M. genitalium testing. It is not recom mended to screen for M. genitalium in those who are asymptomatic. However, sex partners of patients with symptomatic M. genitalium infection should receive testing. Those with positive test results should receive treatment with antibiotics to possibly reduce the risk for reinfection. Macrolides and doxycycline are considered the antimicrobial agents of choice for Ureaplasma infections (Table 193-2). Ure aplasma resistance to macrolides, doxycycline, quinolones, and chloramphenicol has been reported. M. hominis is resistant to mac rolides. Doxycycline is generally the drug of choice for M. hominis infections, although resistance has been reported. Clindamycin is generally active against M. hominis. Quinolones are active in vitro against M. hominis. For M. genitalium, treatment failure and/or antibiotic resistance has increased for both azithromycin and moxifloxacin. The Centers for Disease Control and Prevention’s 2021 Sexually Transmitted Infections Treatment Guidelines recommend two-stage therapy based on antibiotic resistance testing, if available: doxycycline 100 mg orally 2 times per day for 7 days, followed by either azithromycin 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (if macrolide sensitive), or moxifloxacin 400 mg orally once daily for 7 days (if macrolide resistant). If M. genitalium antibiotic resistance testing is not available, then doxycycline fol lowed by moxifloxacin is recommended. Test of cure for M. genita lium infection is not recommended for asymptomatic persons who received treatment with a recommended regimen. CHAPTER 194 Chlamydial Infections ■ ■FURTHER READING Waites KB et al: Mycoplasma pneumoniae from the respiratory tract and beyond. Clin Microbiol Rev 30:747, 2017. Waites KB et al: Macrolide-resistant Mycoplasma pneumoniae in the United States as determined from a national surveillance program. J Clin Microbiol 57:e00968, 2019. Wang G et al: Global prevalence of resistance to macrolides in Myco plasma pneumoniae: A systematic review and meta-analysis. J Anti microb Chemother 77:2353, 2022. Workowski KA et al: Sexually transmitted diseases treatment guide lines, 2021. MMWR Recomm Rep 70:1, 2021. Matthew M. Hamill, Thomas C. Quinn

Chlamydial Infections Chlamydiae are obligate intracellular bacteria that cause a wide variety of diseases in humans and nonhuman animals. ETIOLOGIC AGENTS The chlamydiae were originally

classified as four species in the genus Chlamydia: C. trachomatis, C. pneumoniae, C. psittaci, and C. pecorum (the last species being found in ruminants). The C. psittaci group has been separated into three species: C. psittaci, C. felis, and C. abortus. The mouse pneumonitis strain (MoPn) is now classified as

C. muridarum, and the guinea pig inclusion conjunctivitis strain (GPIC) is now designated C. caviae.

C. trachomatis is divided into two biovars: trachoma and LGV (lym phogranuloma venereum). The trachoma biovar causes two major types of disease in humans: ocular trachoma, the leading infectious cause of preventable blindness in the developing world; and urogenital infections, which are predominantly sexually transmitted but can be neonatally transmitted. The 18 serovars of C. trachomatis fall into three groups: the trachoma serovars A, B, Ba, and C; the oculogenital serovars D–K; and the LGV serovars L1–L3. Serovars can be distinguished by serologic typing with monoclonal antibodies or by molecular gene typing. How ever, serovar identification usually is not important clinically, since the antibiotic susceptibility pattern is the same for all three groups. The one exception applies when LGV is suspected on clinical grounds; in this situation, serovar determination is important because a longer treatment duration is typically required for LGV strains. BIOLOGY, GROWTH CYCLE, AND PATHOGENESIS ■ ■BIOLOGY During their intracellular growth, chlamydiae produce characteristic intracytoplasmic inclusions that can be visualized by direct fluorescent antibody or Giemsa staining of infected clinical material, such as con junctival scrapings or cervical or urethral epithelial cells. Chlamydiae are nonmotile, gram-negative, obligate intracellular bacteria that replicate within the cytoplasm of host cells, forming the characteristic membrane-bound inclusions that are the basis for some diagnostic tests. Originally considered to be large viruses, chlamydiae differ from viruses in possessing RNA and DNA as well as a cell wall that is quite similar in structure to the cell wall of typical gram-negative bacteria. However, chlamydiae lack peptidoglycan; their structural integrity depends on disulfide binding of outer-membrane proteins. PART 5 Infectious Diseases ■ ■GROWTH CYCLE Among the defining characteristics of chlamydiae is a unique growth cycle that involves alternation between two highly specialized morpho logic forms (Figs. 194-1 and 194-2): the elementary body, which is the infectious form and is specifically adapted for extracellular survival, and the metabolically active and replicating reticulate body, which is not infectious, is adapted for an intracellular environment, and does not survive well outside the host cell. The biphasic growth cycle begins with attachment of the elementary body (diameter, 0.25–0.35 μm) at specific sites on the surface of the host cell. The elementary body enters the cell through a process similar to receptor-mediated endocytosis and resides in an inclusion, where the entire growth cycle is completed. The chlamydiae prevent phagosome–lysosome fusion. The inclusion membrane is modified by insertion of chlamydial antigens. Once the elementary body has entered the cell, it reorganizes into a reticulate body, which is larger (0.5–1 μm) and contains more RNA. After ~8 h, the reticulate body starts to divide by binary fission. The intracytoplasmic, membrane-bound inclusion body containing the reticulate bodies increases in size as the reticulate bodies multiply. Approximately 18–24 h after infection of the cell, these reticulate bodies begin to become elementary bodies by a reorganization or condensation pro cess that is poorly understood. After rupture of the inclusion body, the elementary bodies are released to initiate another cycle of infection. Chlamydiae are susceptible to many broad-spectrum antibiotics and possess a number of enzymes, but they have a very restricted metabolic capacity. None of these metabolic reactions result in the production of energy. Chlamydiae have thus been considered to be energy parasites that use the ATP produced by the

host cell for their own metabolic functions. Many aspects of chlamydial molecular biology are not well understood, but the sequencing of several chlamydial genomes and new proteomics research have provided researchers with many relevant tools for elucidating the biology of the life cycle. ■ ■PATHOGENESIS Genital infections are primarily caused by C. trachomatis serovars D–K, with serovars D, E, and F involved most frequently. Molecular

FIGURE 194-1 Chlamydial intracellular inclusions filled with smaller dense elementary bodies and larger reticulate bodies. (Reprinted with permission from WE Stamm: Chlamydial infections, in Harrison's Principles of Internal Medicine, 17th ed. AS Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1070.) 2. Initial inclusions 3. Fusion of inclusions; appearance of RBs

1. Uptake of chlamydial EBs Cell membrane Cell cytoplasm Cell nucleus
2. Multiplication of RBs; enlargement of inclusion
3. Release of EBs
4. Conversion of RBs to EBs
5. Return to normal cycle with IFN-γ removal
6. Persistence associated with IFN-γ exposure; large aberrant RBs FIGURE 194-2 Chlamydial life cycle. EBs, elementary bodies; IFN-γ, interferon γ; RBs, reticulate bodies. (Reproduced with permission from WE Stamm: Chlamydial infections, in AS Fauci et al [eds]: Harrison's Principles of Internal Medicine, 17th ed. New York, McGraw-Hill, 2008.)

typing of the major outer-membrane protein gene (omp1) from which serovar differences arise has been used to demonstrate that polymor phisms can occur in isolates from patients who are exposed frequently to multiple infections, while less variation is observed in isolates from less sexually active populations. Polymorphisms in the major outermembrane protein may provide antigenic variation, and the different forms allow persistence in the community because immunity to one is not protective against the others. The trachoma biovar is essentially a parasite of squamocolumnar epithelial cells; the LGV biovar is more invasive and involves lymphoid cells. As is typical of chlamydiae, C. trachomatis strains are capable of causing chronic, clinically inapparent, asymptomatic infections. Because the duration of the chlamydial growth cycle is ~48–72 h, the incubation period of sexually transmitted chlamydial infections is relatively long—generally 1–3 weeks. C. trachomatis causes cell death as a result of its replicative cycle and can induce cell damage whenever it persists. However, few toxic effects are demonstrated, and cell death because of chlamydial replication is not sufficient to account for dis ease manifestations, the majority of which are due to immunopatho logic mechanisms or nonspecific host responses to the organism or its by-products. In recent years, the entire genomes of various chlamydial species have been sequenced, the field of proteomics has become estab lished, host innate immunity has been more precisely delineated, and innovative host cell–chlamydial interaction studies have been conducted. As a result, many insights have been gained into how chla mydiae adapt and replicate in their intracellular environment and produce disease. These insights into pathogenesis include information on the regulation of gene expression, protein localization, the type III secretion system, the roles of CD4+ and CD8+ T lymphocytes in the host response, and T lymphocyte trafficking. The chlamydial heat-shock protein, which shares antigenic epitopes with similar proteins of other bacteria and with human heat-shock protein, may sensitize the host, and repeated infections may cause host cell damage. Persistent or recurrent chlamydial infections are associ ated with fibrosis, scarring, and complications following simple squa mocolumnar epithelial infections. A common

endpoint of these late consequences is scarring of mucous membranes. Genital complications can lead to pelvic inflammatory disease (PID) and its late consequences of tubal factor infertility, ectopic pregnancy, and chronic pelvic pain, while ocular infections may lead to blinding trachoma. High levels of antibody to human heat-shock protein have been associated with tubal factor infertility and ectopic pregnancy. Without adequate therapy, chlamydial infections may persist for several years, although symptoms— if present—usually abate. Pathogenic mechanisms of C. pneumoniae have yet to be completely elucidated. The same is true for C. psittaci, except that this agent infects cells very efficiently and causes disease that may reflect direct cytopathic effects. C. TRACHOMATIS INFECTIONS ■ ■GENITAL INFECTIONS (SEE ALSO CHAP. 141) Spectrum Although chlamydiae cause a number of human dis eases, localized lower genital tract infections caused by C. trachomatis and the sequelae of such infections are the most important in terms of medical and economic impact. Oculogenital infections due to C. trachomatis serovars D–K are transmitted during sexual contact or from mother to baby during childbirth and are associated with many syndromes, including cervicitis, salpingitis, acute urethral syndrome, endometritis, ectopic pregnancy, infertility, and PID in female patients; urethritis, proctitis, and epididymitis in male patients; and reactive arthritis, conjunctivitis, and pneumonia in infants. Women bear the greatest burden of morbidity because of the serious sequelae of these infections. Untreated infections may lead to PID, and multiple episodes of PID can lead to tubal factor infertility and chronic pelvic pain. Studies estimate that up to 80–90% of women and >50% of men with

C. trachomatis genital infections lack symptoms; other patients have

very mild symptoms. Additionally, extragenital infection in the phar ynx and rectum is typically asymptomatic and may persist for years without treatment. Thus, a large reservoir of infected persons contin ues to transmit infection to sexual partners.

As their designations reflect, the LGV serovars (L1, L2, and L3) cause LGV, an invasive sexually transmitted infection (STI) characterized by a transient and typically painless genital ulcer followed by acute lymph adenitis with bubo formation and/or acute hemorrhagic proctitis (see “Lymphogranuloma Venereum,” below). Epidemiology • GLOBAL EPIDEMIOLOGY C. trachomatis geni tal infections are global in distribution. The World Health Organiza tion (WHO) estimated that in 2020, 50 million (95% uncertainty interval [UI] 36-67) prevalent cases in men and 77 million [UI 67-90] prevalent cases in women and 59 million [95% UI 34-90] new cases of chlamydia in men and 70[95% UI 44-98] new cases in women. These figures make chlamydial infection the most prevalent bacterial STI in the world. There are large differences by WHO region; in 2020 in the Americas, the male incidence (per 1000) was 48 (95% UI, 23–86), compared with 12 (95% UI, 5–25) in Southeast Asia. In women in the Americas, there were 68 (95% UI, 39–104) incident cases (per 1000) compared with 16 (95% UI, 7–28) in Southeast Asia. The associated morbidity is substantial, and the economic cost is high. U.S. EPIDEMIOLOGY In the United States, these infections are the most commonly reported of all infectious diseases. Chlamydia is noti fiable nationally and is reported to the U.S. Centers for Disease Control and Prevention (CDC). In 2022, 1,649,716 cases were reported to the CDC, representing a 5-year decline of 6.2%. As chlamydial infections are typically asymptomatic, case reports are profoundly influenced by screening coverage. The disruptions in STI-related screening, preven tion, and care activities during the COVID-19 pandemic necessitate that the trend for chlamydia surveillance data collected during the pandemic should be interpreted with caution. Higher rates among women than among men reflect the focus on

expansion of screening programs for women during the past 25 years. Use of increasingly sen sitive diagnostic nucleic acid amplification tests, an increased emphasis on case reporting, and improvements in the information systems used have elevated the number of cases reported every year. The CDC and other professional organizations recommend annual screening of all sexually active women <25 years of age and women aged >25 years who are at increased risk of infection, as well as rescreening of previ ously infected individuals at 3 months. Additionally, the CDC recom mends that all pregnant women aged <25 years and those >25 years who are at increased risk be routinely screened for chlamydia during the first prenatal visit. Women who remain at risk for infection should be retested in the third trimester to prevent maternal complications and neonatal infection. In pregnancy, a test-of-cure is recommended 4 weeks after treatment. The 2022 U.S. total case count corresponds to 495 cases per 100,000 population. Women have the highest infec tion rates (621.2 cases per 100,000) compared to the rate among men (363.7 cases per 100,000). With the increased availability of urine test ing and extragenital testing, men—including gay, bisexual, and other men who have sex with men (MSM)—are increasingly being tested for chlamydial infection. From 2021 to 2022, rates of chlamydial infection in men increased by 1.8%, whereas rates in women fell by 1.2% during this period. Chlamydia rates remain highest among adolescents and young adults; in 2022, 57.7% of all cases were reported among persons aged 15–24 years. Chlamydial infection rates vary considerably among different racial and ethnic populations as well as between states. For example, the rate in Louisiana per 100,000 population in 2022 was 788.6, compared with 198.0 in Vermont; the rate among blacks/African Americans was 1113.3 per 100,000 population compared with 100.6 in Asians. CHAPTER 194 Chlamydial Infections The aforementioned statistics are based on case reporting; in 2018, the CDC estimated there were 4 million cases of chlamydia in the United States. Although screening programs have demonstrated reduc tions in PID rates, evidence is lacking to support general screening of young sexually active men. In contrast, sexually active MSM should undergo at least annual screening at anatomically exposed sites. Studies

based on screening surveys estimate that the U.S. prevalence of C. tra chomatis cervical infection was 5.9% and 8.8% among asymptomatic male and female college students, respectively; between 3.3 and 8.3% among prenatal patients; 7% for women seen in family planning clin ics; and >10% for women seen in STI clinics. In a cohort of female college students, incident chlamydial infection was also associated with bacterial vaginosis and high-risk human papillomavirus infection. The prevalence of C. trachomatis in the cervix of pregnant women is approximately six times higher than that of Neisseria gonorrhoeae. The prevalence of genital infection with either agent is highest among women who are between the ages of 20 and 24. Recurrent infections are common in groups with greater vulnerability to STIs and are often acquired from untreated sexual partners. The use of hormonal contraception and the presence of cervical ectopy are also associated with an increased risk. The proportion of infections that are asymp tomatic appears to be higher for C. trachomatis (83.9% in men, 87.1% in women) than for N. gonorrhoeae, (41.3% in men, 68.4% in women), and symptomatic C. trachomatis infections are clinically less severe. Mild or asymptomatic C. trachomatis infections of the fallopian tubes nonetheless cause ongoing tubal damage and infertility. The costs of

C. trachomatis infections and their complications to the U.S. health care system have recently been estimated to be >$516.7 million annually.

Clinical Manifestations • NONGONOCOCCAL AND POSTGONO COCCAL URETHRITIS C. trachomatis is the most common cause of nongonococcal urethritis (NGU) and postgonococcal urethritis (PGU). The designation PGU refers to NGU developing in men 2–3 weeks after treatment of gonococcal urethritis with single doses of agents such as penicillin or cephalosporins, which lack antimicrobial activity against chlamydiae. Current treatment regimens for gonorrhea have evolved and now include combination therapy with ceftriaxone and doxycycline unless chlamydia has been excluded; if chlamydia has been excluded, then gonorrhea is treated with ceftriaxone mono therapy. Thus, both the incidence of PGU and the causative role of C. trachomatis in this syndrome have declined. PART 5 Infectious Diseases In the United States, most of the estimated 2 million cases of acute urethritis are NGU, and C. trachomatis is implicated in 30–50% of these cases. The cause of most of the remaining cases of NGU is due to Myco plasma genitalium; Trichomonas vaginalis and herpes simplex virus (HSV) cause some cases. Other etiologies include Haemophilus species, N. meningitidis, and adenovirus. The rate of involvement of C. tracho matis in urethral infection ranges from 3–7% among asymptomatic men to 15–20% among symptomatic men attending STI clinics. One multisite study of men in Baltimore, Seattle, Denver, and San Francisco reported an overall chlamydial prevalence of 7% in urine samples assessed by nucleic acid amplification tests (NAATs)—molecular tests that amplify the nucleic acids in clinical specimens. As in women, infection in men is age related, with young age most strongly associ ated with chlamydial urethritis. The prevalence among men is highest at 20–24 years of age. In STI clinics, urethritis is usually less prevalent among MSM than among heterosexual men. NGU is diagnosed by documentation of leukocytes on urethral exudate and by exclusion of gonorrhea by Gram's staining, NAAT, or culture. C. trachomatis urethritis is generally less severe than gonococ cal urethritis, although in any individual patient, these two forms of urethritis cannot reliably be differentiated solely on clinical grounds. Symptoms include urethral discharge (often whitish and mucoid rather than frankly purulent), dysuria, and urethral itching. Physical examination may reveal meatal erythema and tenderness as well as a urethral exudate that is often demonstrable only by stripping or milk ing of the urethra. At least one-third of male patients with C. trachomatis urethral infection have no evident signs or symptoms of urethritis. The avail ability of NAATs for first-void urine specimens has facilitated broaderbased testing for asymptomatic infection in male patients. As a result, asymptomatic chlamydial infection has been demonstrated in 5–10% of sexually active male adolescents screened at school-based clinics or community centers. Such patients generally have pyuria (≥15 leuko cytes per 400× microscopic field in the sediment of first-void urine), a

positive leukocyte esterase test, or an increased number of leukocytes on a Gram-stained smear prepared from a urogenital swab inserted 1–2 cm into the anterior urethra. When specific diagnostic tests for chlamydiae are not available, the examination of an endourethral speci men for increased leukocytes is useful in differentiating between true urethritis and functional symptoms in symptomatic patients. Alterna tively, urethritis can be assayed noninvasively by examination of a firstvoid urine sample for pyuria, either by microscopy or by the leukocyte esterase test. Urine (or a urethral swab) can also be tested directly for chlamydiae by DNA amplification methods (NAATs), as described below (see "Detection Methods"). Urine testing for urethral STIs in men is much more acceptable than endourethral swab collection. EPIDIDYMITIS Chlamydial urethritis may be followed by acute epi didymitis (<6 weeks' duration), but this condition is rare, generally occurring in sexually active patients <35 years of age; in older men, epididymitis is usually associated with gram-negative bacterial infec tion and/or instrumentation procedures. An estimated 50–70% of

cases of acute epididymitis are caused by C. trachomatis. The condition usu ally presents as unilateral scrotal pain with tenderness, swelling, and fever in a young man, often occurring in association with chlamydial urethritis. The illness may be mild enough to treat with oral antibiot ics on an outpatient basis or severe enough to require hospitalization and parenteral therapy. Testicular torsion should be excluded promptly by imaging or surgical exploration in a teenager or young adult who presents with acute unilateral testicular pain without urethritis. The possibility of testicular tumor or chronic infection (>6 weeks' duration) (e.g., tuberculosis) should be excluded when a patient with unilateral intrascrotal pain and swelling does not respond to appropriate antimi crobial therapy. REACTIVE ARTHRITIS Reactive arthritis consists of conjunctivitis, urethritis (or, in female patients, cervicitis), arthritis, and characteristic mucocutaneous lesions. It may develop in 1–2% of cases of NGU; the rate of chlamydia-induced arthritis has been estimated to be 4–15% and is thought to be the most common type of peripheral inflamma tory arthritis in young men. When reactive arthritis is triggered by an STI, it may also be referred to as sexually acquired reactive arthri tis (SARA). C. trachomatis has been recovered from the urethra of 16–44% of patients with reactive arthritis and 69% of men with signs of urogenital inflammation at the time of examination. Antibodies to C. trachomatis have also been detected in 46–67% of patients with reactive arthritis, and Chlamydia-specific cell-mediated immunity has been documented in 72%. In addition, C. trachomatis has been isolated from synovial biopsy samples from 15 of 29 patients in a number of small series and from a smaller proportion of synovial fluid specimens. Chlamydial nucleic acids have been identified in synovial membranes and chlamydial elementary bodies in joint fluid. The pathogenesis of reactive arthritis is unclear, but this condition probably represents an abnormal host response to a number of infectious agents, including those associated with bacterial gastroenteritis (e.g., Salmonella, Shigella, Yersinia, or Campylobacter), or to infection with C. trachomatis or N. gonorrhoeae. An association between reactive arthritis and the HLA-B27 phenotype in white individuals has been described, but not in patients from sub-Saharan Africa, where the prevalence of HLAB27 is much lower. Since other mucosal infections produce an identi cal syndrome, chlamydial infection is thought to initiate an aberrant hyperreactive immune response that produces inflammation of the involved target organs in these genetically predisposed individuals. Evidence of exaggerated cell-mediated and humoral immune responses to chlamydial antigens in reactive arthritis supports this hypothesis. The finding of chlamydial elementary bodies and DNA in joint fluid and synovial tissue from patients with reactive arthritis suggests that chlamydiae may actually spread from genital to joint tissues in these patients—perhaps in macrophages. NGU is the initial manifestation of reactive arthritis in 80% of patients, typically occurring within 14 days after sexual exposure. The urethritis may be mild and may even go unnoticed by the patient. Similarly, gonococcal urethritis may precede reactive arthritis, but coinfection with an agent of NGU is difficult to rule out. The urethral

discharge may be purulent or mucopurulent, and patients may or may not report dysuria. Accompanying prostatitis, usually asymptomatic, has been described. Arthritis usually begins ~4 weeks after the onset of urethritis but may develop sooner or, in a small percentage of cases, may actually precede urethritis. The knees are most frequently involved; next most commonly affected are the ankles and small joints of the feet. Sacroiliitis, either symmetrical or asymmetrical, is docu mented in two-thirds of patients. Mild bilateral conjunctivitis, iritis, keratitis, or uveitis is sometimes present but lasts for only a few days. Finally, dermatologic manifestations occur in up to 50% of patients. The initial lesions—usually papules with a central yellow spot—most often involve the soles and palms and, in ~25% of patients, eventually epithelialize and thicken to produce

keratoderma blenorrhagicum. Circinate balanitis is usually painless and occurs in fewer than half of patients. The initial episode of reactive arthritis usually lasts 2–6 months. PROCTITIS Primary anal or rectal infections with C. trachomatis have been described in women and MSM who practice receptive anal intercourse. Symptoms are characterized by anorectal pain, a bloody mucopurulent discharge, and tenesmus. Oculogenital serovars D–K and LGV serovars L1, L2, and L3 have been found to cause proctitis. The LGV serovars are far more invasive and typically cause more severely symptomatic disease, including severe ulcerative proctocolitis that can be clinically confused with HSV proctitis. However, asymptomatic or paucisymptomatic LGV infection is increasingly recognized in MSM. Histologically, LGV proctitis may resemble Crohn's disease in that giant cell formation and granulomas are detected. In the United States and Europe, cases of LGV proctitis occur almost exclusively in MSM, many of whom have HIV infection and other STI coinfections. The less invasive non-LGV serovars of C. trachomatis cause mild proctitis. Many infected individuals are asymptomatic, and in these cases, infection is diagnosed only by routine NAAT of rectal swabs. The number of fecal leukocytes is usually abnormal in both asymptomatic and symptomatic cases. Sigmoidoscopy may yield normal findings or may reveal mild inflammatory changes or small erosions or follicles in the lower 10 cm of the rectum. Histologic examination of rectal biopsies generally shows anal crypts and prominent follicles as well as neutrophilic infiltration of the lamina propria. Chlamydial proctitis is best diagnosed by isolation of C. trachomatis from the rectum and documentation of a response to appropriate therapy. NAATs are the diagnostic test of choice. MUCOPURULENT CERVICITIS Although most women with chla mydial infections of the cervix have no symptoms, almost half gener ally have local signs of infection on examination. Cervicitis is usually characterized by the presence of a mucopurulent discharge, with >20 neutrophils per microscopic field visible in strands of cervical mucus in a thinly smeared, Gram-stained preparation of endocervical exudate. Hypertrophic ectopy of the cervix may also be evident as an edematous area near the cervical os that is congested and bleeds easily on minor trauma (e.g., when a specimen is collected with a swab). A Papanico laou smear shows increased numbers of neutrophils as well as a char acteristic pattern of mononuclear inflammatory cells, including plasma cells, transformed lymphocytes, and histiocytes. Cervical biopsy shows a predominantly mononuclear cell infiltrate of the subepithelial stroma. Clinical experience and collaborative studies indicate that a cutoff of >30 polymorphonuclear leukocytes (PMNs)/1000× field in a Gram-stained smear of cervical mucus correlates best with chlamydial or gonococcal cervicitis. However, the wide availability of NAATs and limited access to microscopy outside of specialist centers has decreased the role of cervical mucus examination. Clinical recognition of chlamydial cervicitis depends on a high index of suspicion and careful cervical examination. No genital symp toms are specifically correlated with chlamydial cervical infection. The differential diagnosis of a mucopurulent discharge from the endocer vical canal in a young, sexually active woman includes gonococcal endocervicitis, salpingitis, endometritis, and intrauterine contraceptive device–induced inflammation. Diagnosis of cervicitis is based on the presence of PMNs on a cervical swab as noted above; the presence of chlamydiae is confirmed by NAAT.

PELVIC INFLAMMATORY DISEASE Inflammation of sections of the fal lopian tube is often referred to as salpingitis or PID. The proportion of acute salpingitis cases caused by C. trachomatis varies geographically and with the population studied. It has been estimated that C. tracho matis causes up to 50% of PID cases in the United States. Recent studies report that the proportions of PID cases attributable to N. gonorrhoeae or C. trachomatis is decreasing; approximately 50% of women diag nosed with acute PID tested positive for either organism. PID occurs via ascending intraluminal

spread of C. trachomatis or N. gonorrhoeae from the lower genital tract. Mucopurulent cervicitis is often followed by endometritis, endosalpingitis, and finally pelvic peritonitis. Evidence of mucopurulent cervicitis is often found in women with laparoscopi cally verified salpingitis. Similarly, endometritis, demonstrated by an endometrial biopsy showing plasma cell infiltration of the endometrial epithelium, is documented in most women with laparoscopy-verified chlamydial (or gonococcal) salpingitis. Chlamydial endometritis can also occur in the absence of clinical evidence of salpingitis. Histologic evidence of endometritis has been correlated with a syndrome consist ing of vaginal bleeding, lower abdominal pain, and uterine tenderness in the absence of adnexal tenderness. Chlamydial salpingitis produces milder symptoms than gonococcal salpingitis and may be associated with less marked adnexal tenderness. Thus, mild adnexal or uterine tenderness in a sexually active woman with cervicitis may suggest chlamydial PID.

Screening and treating sexually active women for chlamydia and gonorrhea reduce their risk for PID. Chronic untreated endometrial and tubal inflammation can result in tubal scarring, impaired tubal function, tubal occlusion, and infertility, even among women who report no prior treatment for chlamydial infection. C. trachomatis has been particularly implicated in “subclinical” PID on the basis of a lack of history of PID among Chlamydia-seropositive women with tubal damage and detection of chlamydial DNA or antigen among asymp tomatic women with tubal infertility. These data suggest that the best method to prevent PID and its sequelae is surveillance and control of lower genital tract infections along with diagnosis and treatment of sex partners and prevention of reinfections. Promotion of early symptom recognition and health care presentation may reduce the frequency and severity of sequelae of PID. CHAPTER 194 Chlamydial Infections PERIHEPATITIS Fitz-Hugh–Curtis syndrome was originally described as a complication of gonococcal PID. However, studies over the past several decades have suggested that chlamydial infection is more com monly associated with perihepatitis than is N. gonorrhoeae. Perihepati tis should be suspected in young, sexually active women who develop right-upper-quadrant pain, fever, or nausea. Evidence of salpingitis may or may not be found on examination. Frequently, perihepatitis is strongly associated with extensive tubal scarring, adhesions, and inflammation observed at laparoscopy, and high titers of antibody to the 57-kDa chlamydial heat-shock protein have been documented. Culture and/or serologic evidence of C. trachomatis has been found in three-fourths of women with this syndrome. URETHRAL SYNDROME IN WOMEN In the absence of infection with uropathogens such as coliforms or Staphylococcus saprophyticus, C. tra chomatis is the pathogen most commonly isolated from college women with dysuria, frequency, and pyuria. Screening studies can recover C. trachomatis at both the cervix and the urethra; in up to 25% of infected women, the organism is isolated only from the urethra. The urethral syndrome in women consists of dysuria and frequency in conjunction with chlamydial urethritis, pyuria, and no bacteriuria or urinary patho gens. Although symptoms of the urethral syndrome may develop in some women with chlamydial infection, the majority of women attend ing STI clinics for urethral chlamydial infection do not have dysuria or frequency. Even in women with chlamydial urethritis causing the acute urethral syndrome, signs of urethritis such as urethral discharge, meatal redness, and swelling are uncommon. However, mucopurulent cervicitis in a woman presenting with dysuria and frequency strongly suggests C. trachomatis urethritis. Other correlates of chlamydial urethral syndrome include a duration of dysuria of >7–10 days, lack of hematuria, and lack of suprapubic tenderness. Abnormal urethral

Gram’s stains showing >10 PMNs/1000× field in women with dysuria but without coliform bacteriuria support the diagnosis of chlamydial urethritis. Other possible diagnoses include gonococcal or trichomonal infection of the urethra.

INFECTION IN PREGNANCY AND THE NEONATAL PERIOD Infections during pregnancy can be transmitted to infants during delivery. Approximately 20–30% of infants exposed to C. trachomatis in the birth canal develop conjunctivitis, and 10–15% subsequently develop pneumonia. All newborn infants receive ocular prophylaxis at birth to prevent ophthalmia neonatorum. The agents used to prevent gonococ cal eye infection are not effective against chlamydial conjunctivitis. The most effective measure to prevent neonatal chlamydial conjunc tivitis is through screening and treatment of chlamydial infections in pregnant women. Without treatment, conjunctivitis usually develops at 5–19 days of life and often results in a profuse mucopurulent dis charge. Roughly half of infected infants develop clinical evidence of inclusion conjunctivitis. However, it is impossible to differentiate chlamydial conjunctivitis from other forms of neonatal conjunctivitis (e.g., that due to N. gonorrhoeae, Haemophilus influenzae, Streptococcus pneumoniae, or HSV) on clinical grounds; thus, laboratory diagnosis is required. Inclusions within epithelial cells are often detected in Giemsa-stained conjunctival smears, but these smears are considerably less sensitive than cultures or NAATs for chlamydiae. Gram-stained smears may show gonococci or occasional small gram-negative coc cobacilli in Haemophilus conjunctivitis, but smears should be accom panied by cultures or NAATs for these agents. C. trachomatis has also been isolated frequently and persistently from the nasopharynx, rectum, and vagina of infected infants—occa sionally for >1 year in the absence of treatment. In some cases, otitis media results from perinatally acquired chlamydial infection. Pneumo nia may develop in infants from 2 weeks to 4 months of age. C. tracho matis is estimated to cause 20–30% of pneumonia cases in infants <6 months of age. Epidemiologic studies have linked chlamydial pul monary infection in infants with increased occurrence of subacute lung disease (bronchitis, asthma, wheezing) in later childhood. PART 5 Infectious Diseases LYMPHOGRANULOMA VENEREUM C. trachomatis serovars L1, L2, and L3 cause LGV, an invasive systemic STI. The peak incidence of LGV corresponds with the age of greatest sexual activity: the second and third decades of life. The worldwide incidence of LGV is falling, but the disease is still endemic and a major cause of morbidity in parts of Asia, Africa, South America, and the Caribbean. LGV is rare in indus trialized countries; for more than a decade, the reported incidence in the United States has been only 0.1 case per 100,000 population. In the Bahamas, an apparent outbreak of LGV was described in association with a concurrent increase in heterosexual infection with HIV. Reports of outbreaks with the newly identified variant L2b in Europe, Australia, and the United States indicate that LGV is becoming more prevalent among MSM. These cases have usually presented as hemorrhagic proc tocolitis in HIV-positive men. However, LGV is increasingly described as an asymptomatic rectal infection in 30–50% of cases and is fre quently seen in MSM without HIV. More widespread use of NAATs for identification of rectal infections may have enhanced case recognition. LGV begins as a small painless papule that tends to ulcerate at the site of inoculation, often escaping attention. This primary lesion heals in a few days without scarring and is usually recognized as LGV only in retrospect. LGV strains of C. trachomatis have occasionally been recov ered from genital ulcers and from the urethra of men and the endo cervix of women who present with inguinal adenopathy; these areas may be the primary sites of infection in some cases. Proctitis is more common among people who practice receptive anal intercourse, and an elevated white blood cell count in anorectal smears may predict LGV in these patients. Ulcer formation may facilitate transmission of HIV infection and other sexually transmitted and

blood-borne infections. As NAATs for C. trachomatis are standard of care in high-income settings, increasing numbers of cases of LGV proctitis are being rec ognized in MSM. Such patients present with anorectal pain and muco purulent, bloody rectal discharge. Sigmoidoscopy reveals ulcerative proctitis or proctocolitis, with purulent exudate and mucosal bleeding.

Histopathologic findings in the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. These clinical, sigmoidoscopic, and histopathologic findings may closely resemble those of Crohn’s disease of the rectum. The most common presenting picture in heterosexual men and women is the inguinal syndrome, which is characterized by pain ful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure; in rare instances, the onset comes after a few months. The inguinal adenopathy is unilateral in two-thirds of cases, and palpable enlargement of the iliac and femoral nodes is often evident on the same side as the enlarged inguinal nodes. The nodes are initially dis crete, but progressive periadenitis results in a matted mass of nodes that becomes fluctuant and suppurative. The overlying skin becomes fixed, inflamed, and thin, and multiple draining fistulas finally develop. Extensive enlargement of chains of inguinal nodes above and below the inguinal ligament (“the groove sign”) is not specific and, although not uncommon, is documented in only a minority of cases. Spontane ous healing usually takes place after several months; inguinal scars or granulomatous masses of various sizes persist for life. Massive pelvic lymphadenopathy may lead to exploratory laparotomy. Constitutional symptoms are common during the stage of regional lymphadenopathy and, in cases of proctitis, may include fever, chills, headache, meningismus, anorexia, myalgias, and arthralgias. Other systemic complications are infrequent but include arthritis with ster ile effusion, aseptic meningitis, meningoencephalitis, conjunctivitis, hepatitis, and erythema nodosum (Fig. A1-39). Complications of untreated anorectal infection include perirectal abscess; anal fistulas; and rectovaginal, rectovesical, and ischiorectal fistulas. Secondary bacterial infection probably contributes to these complications. Rectal stricture is a late complication of anorectal infection and usually devel ops 2–6 cm from the anal orifice—i.e., at a site within reach on digital rectal examination. A small percentage of cases of LGV in men present as chronic progressive infiltrative, ulcerative, or fistular lesions of the penis, urethra, or scrotum. Associated lymphatic obstruction may pro duce elephantiasis. When urethral stricture occurs, it usually involves the posterior urethra and causes incontinence or difficulty with urina tion. In women, esthiomene of the genitalia is a late, rare complication of untreated LGV infection resulting in massive labial elephantiasis and ulceration followed by scarring. Diagnosis • DETECTION METHODS Historically, chlamydiae were cultivated in the yolk sac of embryonated eggs. The organisms can be grown more easily in tissue culture, but cell culture—once con sidered the diagnostic gold standard—has been replaced by nonculture assays (Table 194-1). In general, culture for chlamydiae in clinical specimens is now performed only in specialized laboratories. The first nonculture assays, such as direct fluorescent antibody staining of clinical material and enzyme immunoassay (EIA), have been replaced by NAATs, which are currently recommended by the CDC as the diagnostic assays of choice. At present, numerous NAAT assays cleared by the U.S. Food and Drug Administration (FDA) are commercially available, some of which are available as high-throughput robotic plat forms. Three point-of-care rapid diagnostic assays are available; they are of increasing interest since patients can potentially be treated before leaving the clinic, thus preventing forward transmission while patients wait for results from tests with longer turnaround times. However, turnaround time and cost of goods currently limit their widespread adoption. Over-the-counter tests are also in development. CHOICE OF SPECIMEN Cervical and urethral swabs have traditionally been used for the diagnosis of STIs in

female and male patients, respec tively. However, given the greatly increased sensitivity and specificity of NAATs, less invasive samples (e.g., urine for both sexes and vaginal swabs for women) can be used. For screening of women, the CDC now recommends that self-collected or clinician-collected vaginal swabs, which are slightly more sensitive than urine, be used; a recent analysis demonstrated the superiority of vaginal swabs over urine in women. Urine screening tests are often used in outreach screening programs, however. For symptomatic women undergoing a pelvic examination, cervical swab samples may be used because they have slightly higher

TABLE 194-1 Diagnostic Tests for Sexually Transmitted and Perinatal Chlamydia trachomatis Infection INFECTION SUGGESTIVE SIGNS/SYMPTOMS PRESUMPTIVE DIAGNOSISa CONFIRMATORY TEST OF CHOICE Men NGU, PGU Discharge, dysuria Gram's stain with ≥2 WBCs/high power field (HPF) in highprevalence settings (e.g., STI clinics) or ≥5 WBCs/HPF in lower-prevalence settings. No gram-negative intracellular diplococci (GNID). In the absence of microscopy: positive leukocyte esterase test on first catch urine Epididymitis Unilateral intrascrotal swelling, pain, tenderness; fever; NGU Gram's stain with ≥2 (or ≥5) WBCs/HPF; no GNID; urinalysis with pyuria Women Cervicitis Mucopurulent cervical discharge, sustained endocervical bleeding easily induced by nontraumatic passage of a swab through the cervical os Leukorrhea, defined as >10 WBCs/HPF on microscopic examination of vaginal fluid, might be a sensitive indicator of cervical inflammation with a high negative predictive value Salpingitis Lower abdominal pain, cervical motion tenderness, adnexal tenderness or masses C. trachomatis always potentially present in salpingitis Vaginal (or cervical) NAAT for C. trachomatis Urethritis Dysuria and frequency without hematuria MPC; sterile pyuria; negative routine urine culture Urine NAAT for C. trachomatis Adults of Either Sex Proctitis Rectal pain, discharge, tenesmus, bleeding; history of receptive anorectal intercourse Negative gonococcal NAAT and Gram's stain; at least 1 WBC/HPF in rectal Gram's stain Reactive arthritis NGU, arthritis, conjunctivitis, typical skin lesions Gram's stain with ≥5 WBC/HPF; lack of GNID Urine or vaginal NAAT for C. trachomatis LGV Regional adenopathy, primary lesion, proctitis, systemic symptoms None NAAT for C. trachomatis. Molecular testing for LGV is not widely available or not FDA cleared. If available, molecular PCR testing for C. trachomatis serovars L1, L2, or L3 can confirm diagnosis LGV Neonates Conjunctivitis Purulent conjunctival discharge 5–12 days after birth Negative culture and Gram's stain for gonococci, Haemophilus spp., pneumococci, staphylococci Infant pneumonia Subacute, afebrile pneumonia in infants aged 1–3 months None Chlamydial tissue culture, DFA, or NAAT (not FDA cleared) of nasopharyngeal specimen aA presumptive diagnosis of chlamydial infection is often made in the syndromes listed when gonococci are not found. A positive test for Neisseria gonorrhoeae does not exclude the involvement of C. trachomatis, which often is present in patients with gonorrhea. Abbreviations: DFA, direct fluorescent antibody; FDA, U.S. Food and Drug Administration; HPF, high-power field; LGV, lymphogranuloma venereum; MPC, mucopurulent cervicitis; NAAT, nucleic acid amplification test; NGU, nongonococcal urethritis; PGU, postgonococcal urethritis; WBC, white blood cell. Source: Based on Centers for Disease Control and Prevention Sexually Transmitted Infections Treatment Guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/ STI-Guidelines-2021.pdf.
chlamydial counts. For male patients, a first-catch urine specimen is the sample of choice, but self-collected penile-meatal swabs have been shown to be very effective. ALTERNATIVE SPECIMEN TYPES Ocular samples from babies and adults can be assessed by NAATs. However, NAATs are not cleared by the FDA for detecting chlamydia from conjunctival swabs, and clinical laboratories should verify the procedure according to Clini cal Laboratory Improvement Amendments regulations. Samples from extragenital rectal and pharyngeal sites are used to detect chlamydiae

by NAATs; in 2019, the CDC cleared the first NAATS for use on extra genital samples. OTHER DIAGNOSTIC ISSUES Because NAATs detect nucleic acids instead of live organisms, they should be used with caution as testof-cure assays. Residual nucleic acid from cells rendered noninfective by antibiotics may continue to yield a positive result in NAATs for as long as 3 weeks after therapy when viable organisms have actually been eradicated. Therefore, clinicians should not use NAATs for test of cure until after 3 weeks. The CDC currently does not recommend a test of cure after treatment for infection with C. trachomatis except in pregnancy. However, because incidence studies have demonstrated that previous chlamydial infection increases the probability of becoming

Urine NAAT for C. trachomatis Urine NAAT for C. trachomatis Vaginal (or cervical) NAAT for C. trachomatis Rectal NAAT for C. trachomatis CHAPTER 194 Chlamydial Infections Tissue culture, conjunctival NAAT for C. trachomatis (not FDA cleared); DFA-stained scraping of conjunctival material reinfected, the CDC does recommend that previously infected indi viduals be rescreened 3 months after treatment. SEROLOGY Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by C. trachomatis. The serologic test of choice is the microimmunofluorescence (MIF) test, in which high-titer purified elementary bodies mixed with embryonated chicken yolk sac material are affixed to a glass microscope slide to which dilutions of sera are applied. After incubation and washing, fluorescein-conjugated IgG or IgM antibody is applied. The test is read with an epifluorescence microscope, with the highest dilution of serum producing visible fluorescence designated as the titer. The MIF test is not widely available except in research laboratories and is highly labor intensive. Although the complement fixation (CF) test can also be used, it employs lipopolysaccharide (LPS) as the antigen and therefore identifies the pathogen only to the genus level. Single-point titers of >1:64 support a diagnosis of LGV, for which it is difficult to demonstrate rising antibody titers—i.e., paired serum samples are difficult to obtain since the disease often results in the patient’s being seen by the physician after the acute stage. Any anti body titer of >1:16 is considered significant evidence of exposure to chlamydiae. However, serologic testing is never recommended for

diagnosis of uncomplicated genital infections of the cervix, urethra, and lower genital tract or for C. trachomatis screening of asymptom atic individuals.

TREATMENT C. trachomatis Genital Infections A 7-day course of oral doxycycline (100 mg twice daily) is the recommended regimen of treatment for uncomplicated chlamydial infections. A single 1-g oral dose of azithromycin or oral levofloxa cin 500 mg once daily for 7 days are alternatives. Doxycycline has slightly better efficacy than azithromycin in treatment of genital chlamydia infection and has demonstrated significantly higher microbiological cure rates in the treatment of rectal infection. The single-dose regimen of azithromycin has great appeal for the treatment of patients with uncomplicated chlamydial infection (especially those without symptoms and those with a likelihood of adherence challenges) and of the sexual partners of infected patients. These advantages must be weighed against the lower efficacy and greater cost of azithromycin. Whenever possible, the single 1-g dose should be given as directly observed therapy. Although not approved by the FDA for use in pregnancy, this regi men appears to be safe and effective for this purpose. Amoxicillin (500 mg three times daily for 7 days) can also be given as an alterna tive to pregnant women. The fluoroquinolones are contraindicated in pregnancy. A 2-week course of treatment is recommended for complicated chlamydial infections (e.g., PID, epididymitis). Tradi

tionally, a 3-week course of doxycycline (100 mg orally twice daily), azithromycin 1 g orally once weekly for 3 weeks, or erythromycin base (500 mg orally four times daily) is recommended treatment for both bubonic and anogenital LGV. However, several studies have demonstrated the efficacy of shorter-course treatment for LGV. Failure of treatment with a tetracycline in genital infections usually indicates limited adherence or reinfection rather than involvement of a drug-resistant strain. To date, clinically significant drug resis tance has not been observed in C. trachomatis. PART 5 Infectious Diseases Treatment or testing for chlamydiae should be considered among patients with N. gonorrhoeae because of the frequency of coinfection. Systemic treatment with erythromycin base or ethylsuc cinate has been recommended for ophthalmia neonatorum and for C. trachomatis pneumonia in infants. Data on azithromycin efficacy are limited, but it may be effective for use in neonates. For the treatment of adult inclusion conjunctivitis, a single 1-g dose of azithromycin was as effective as standard 10-day treatment with doxycycline. SEX PARTNERS The continued high prevalence of chlamydial infections in most parts of the United States is due primarily to the failure to diag nose—and therefore treat—patients with symptomatic or asymp tomatic infection and their sex partners. Urethral or cervical infection with C. trachomatis has been well documented in a high proportion of the sex partners of patients with NGU, epididymitis, reactive arthritis, salpingitis, and endocervicitis. If possible, con firmatory laboratory tests for chlamydiae should be undertaken in these individuals, but even persons without positive tests or evi dence of clinical disease who have recently been exposed to proven or possible chlamydial infection (e.g., NGU) should be offered therapy. A novel approach is partner-delivered therapy, in which index patients receive treatment and are also provided with treat ment to give to their sex partner(s). NEONATES AND INFANTS In neonates with conjunctivitis or infants with pneumonia, eryth romycin ethylsuccinate or base can be given orally at a dosage of

50 mg/kg per day, preferably in four divided doses, for 2 weeks. Careful attention must be given to adherence to therapy—a fre quent problem. Relapses of eye infection may follow oral erythro mycin therapy. Thus, careful follow-up is required after treatment;

the efficacy of erythromycin treatment for ophthalmia neonatorum is ~80%; therefore, a second course of therapy might be required. Both parents should be examined for C. trachomatis infection and, if diagnostic testing is not readily available, should be treated with doxycycline or azithromycin. Prevention Since many chlamydial infections are asymptomatic, effective control and prevention must involve periodic screening of individuals at risk. Selective cost-effective screening criteria have been developed. Among women, young age (generally <25 years) is a critical risk factor for chlamydial infections in nearly all studies. Other risk factors include mucopurulent cervicitis; multiple, new, or symptomatic male sex partners; and lack of barrier contraceptive use. In some settings, screening based on young age may be as sensitive as criteria that incorporate behavioral and clinical measures. Another strategy is universal testing of all patients in high-prevalence clinic populations (e.g., STI clinics, juvenile detention facilities, and family planning clinics). The effectiveness of selective screening in reducing the prevalence of chlamydial infection among women has been demonstrated in several studies. In the Pacific Northwest, where extensive screening began in family planning clinics in 1998 and in STI clinics in 1993, the preva lence declined from 10% in the 1980s to <5% in 2000. Similar trends have occurred in association with screening programs elsewhere. In addition, screening can reduce upper genital tract disease. In Seattle, women at a large health maintenance organization who were screened for chlamydial infection on a routine basis had a lower incidence of symptomatic PID than did women who

received standard care and underwent more selective screening. In settings with low to moderate prevalence, the prevalence at which selective screening becomes more cost-effective than universal screening must be defined. Most studies have concluded that univer sal screening is preferable in settings with a chlamydial prevalence of

> 3–7%. Depending on the criteria used, selective screening is likely to be more cost-effective when prevalence falls below 3%. The avail ability of highly sensitive and specific diagnostic NAATs using urine specimens and self-obtained vaginal swabs makes it feasible to mount an effective nationwide Chlamydia control program, with screening of individuals with increased vulnerability for STI acquisition in tradi tional health care settings and in novel outreach and community-based settings. The U.S. Preventive Services Task Force has named Chlamydia screening as a Grade B recommendation, which means that private insurance and Medicare will cover the cost of screening under the Affordable Care Act. More recently, home-based, self-collected, mailin testing platforms have expanded the testing for chlamydia and other STIs outside of clinical settings. Since 2018, data have emerged on the efficacy of doxycycline postexposure prophylaxis. Efficacy data exist for MSM and transgender women, where a 200-mg single oral dose of doxycycline taken within 24–72 h of condomless sex reduced the risk of chlamydia acquisition by ~70–80%. ■ ■TRACHOMA Epidemiology Trachoma—a sequela of ocular disease predomi nantly in resource-limited areas—continues to be a leading cause of preventable infectious blindness worldwide. The WHO estimates that ~6 million people have been blinded by trachoma and that ~1.3 million people in developing countries still suffer from preventable blindness due to trachoma; certainly, hundreds of millions live in trachomaendemic areas. Foci of trachoma persist in Africa, Asia, Latin America, the Middle East, and the Pacific Rim. C. trachomatis serovars A, B, Ba, and C are isolated from patients with clinical trachoma in areas of endemicity in countries in Africa, the Middle East, Asia, and South America. The trachoma-hyperendemic areas of the world are in northern and sub-Saharan Africa, the Middle East, drier regions of the Indian sub continent, and Southeast Asia. In hyperendemic areas, the prevalence of trachoma is essentially 100% by the second or third year of life. Active disease is most common among young children, who are the

reservoir for trachoma. By adulthood, active infection is infrequent, but sequelae result in blindness. In such areas, trachoma constitutes the major cause of blindness. Trachoma is transmitted through contact with discharges from the eyes of infected patients. Transmission is most common under poor hygienic conditions and most often takes place between fam ily members or between families with shared facilities. Eye-seeking flies (e.g., Musca sorbens) can also transfer the mucopurulent ocular discharges, carrying the organisms on their legs from one person to another. The International Trachoma Initiative founded by the WHO in 1998 aimed to eliminate blinding trachoma globally by 2020. The Neglected Tropical Disease road map 2021–2030 has set 2030 as the new target year for global elimination of trachoma as a public

health problem. Clinical Manifestations The clinical manifestations of trachoma include two phases: active trachoma (conjunctivitis) and cicatricial disease (conjunctival scarring). Both endemic trachoma and adult inclusion conjunctivitis present initially as conjunctivitis characterized by small lymphoid follicles in the conjunctiva. In regions with hyperen demic classic blinding trachoma, the disease usually starts insidiously before the age of 2 years. Reinfection is common and probably contrib utes to the pathogenesis of trachoma. Studies using polymerase chain reaction (PCR) or other NAATs indicate that chlamydial DNA is often present in the ocular secretions of patients with trachoma, even in the absence of positive cultures. Thus, persistent infection may be more common than was previously thought. The cornea becomes involved, with inflammatory leukocytic infil trations and superficial vascularization (pannus formation). As the inflammation continues, conjunctival scarring eventually distorts the eyelids, causing them to turn inward so that the lashes constantly abrade the eyeball (trichiasis and entropion); eventually the corneal epithelium is abraded and may ulcerate, with subsequent corneal scarring, opacification, and blindness. Destruction of the conjunctival goblet cells, lacrimal ducts, and lacrimal gland may produce a “dry-eye” syndrome, with resultant corneal opacity due to drying (xerosis) or secondary bacterial corneal ulcers. Communities with blinding trachoma often experience seasonal epidemics of conjunctivitis due to H. influenzae that contribute to the intensity of the inflammatory process. In such areas, the active infec tious process usually resolves spontaneously in affected persons at 10–15 years of age, but conjunctival scars continue to shrink, produc ing trichiasis and entropion with subsequent corneal scarring in adults. In areas with milder and less prevalent disease, the process may be much slower, with active disease continuing into adulthood; blindness is rare in these cases. Eye infection with oculogenital C. trachomatis strains in sexually active young adults presents as an acute onset of unilateral follicular conjunctivitis and preauricular lymphadenopathy similar to that seen in acute conjunctivitis caused by adenovirus or HSV. If untreated, the disease may persist for 6 weeks to 2 years. It is frequently associated with corneal inflammation in the form of discrete opacities (“infil trates”), punctate epithelial erosions, and minor degrees of superficial corneal vascularization. Very rarely, conjunctival scarring and eyelid distortion occur, particularly in patients treated for many months with topical glucocorticoids. Recurrent eye infections develop most often in patients whose sexual partners are not treated with antimicrobial agents. Diagnosis The clinical diagnosis of classic trachoma can be made if two of the following signs are present: (1) lymphoid follicles on the upper tarsal conjunctiva; (2) typical conjunctival scarring; (3) vascular pannus; or (4) limbal follicles or their sequelae, Herbert pits. The clinical diagnosis of endemic trachoma should be confirmed by laboratory tests in children with relatively marked degrees of inflam mation. Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears in such populations, but chlamydial NAATs are more sensitive and are often positive when smears or cultures are negative. While NAATS are the most sensitive

and specific diagnostic assays they are prohibitively expensive and require laboratory infrastructure that are not available in most endemic regions. Follicular conjunctivitis in European or American adults living in trachomatous regions is rarely due to trachoma.

TREATMENT Trachoma Adult inclusion conjunctivitis responds well to treatment with the same regimens used in uncomplicated genital infections—namely, azithromycin (a 1-g single oral dose) or doxycycline (100 mg twice daily for 7 days). Chlamydial resistance to azithromycin has not been documented. Topical tetracycline (1% eye ointment twice daily for 6 weeks) can be used as an alternative, but adherence rates are likely to be suboptimal. In the setting of eye infection with

oculogenital strains, simultaneous treatment of all sexual partners is necessary to prevent ocular reinfection and chlamydial genital disease. Topical antibiotic treatment is not required for patients who receive systemic antibiotics. PSITTACOSIS Psittacine birds and many other avian species act as natural reser voirs for C. psittaci–type organisms, common pathogens in domestic mammals and birds. The species C. psittaci, which now includes only avian strains, affects humans only as a zoonosis. (The other strains previously included in this species have been placed into different species that reflect the animals they infect: C. abortus,

C. muridarum, C. suis, C. felis, and C. caviae.) Although all birds are susceptible, pet birds (parrots, parakeets, macaws, and cockatiels) and poultry (turkeys and ducks) are most frequently involved in transmission of C. psittaci to humans. Exposure is greatest in poul try-processing workers and in owners of pet birds. Infectious forms of the organisms are shed from both symptomatic and apparently healthy birds and may remain viable for several months. C. psittaci can be transmitted to humans by direct contact with infected birds or by inhalation of aerosols from avian nasal discharges and from infectious avian fecal or feather dust. Transmission from person to person has never been demonstrated. CHAPTER 194 Chlamydial Infections The diagnosis is usually established serologically. Psittacosis in humans may present as acute primary atypical pneumonia (which can be fatal in up to 10% of untreated cases); as severe chronic pneumonia; or as a mild illness or asymptomatic infection in persons exposed to infected birds. ■ ■EPIDEMIOLOGY True incidence and prevalence of psittacosis is difficult to ascertain, in part due to lack of routine testing and the varying performance of commonly used diagnostic tests. Since 2010, the CDC has typically received 10 reports annually of confirmed cases of psittacosis, although many more cases probably occur than are reported. Outbreaks have been observed in, for example, poultry plant workers. Control of psit tacosis depends on control of avian sources of infection. A pandemic of psittacosis was once stopped by banning shipment or importation of psittacine birds. Birds can receive prophylaxis in the form of a tetracycline-containing feed. Imported birds are currently quarantined for 30 days of treatment. ■ ■CLINICAL MANIFESTATIONS Typical symptoms include fever, chills, muscular aches and pains, severe headache, hepato- and/or splenomegaly, and gastrointestinal symptoms. Hepatitis and neurologic complications can occur. Cardiac complications may involve endocarditis and myocarditis. Fatal cases were common in the preantibiotic era. As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare. Severe pneumonia requiring management in an intensive care unit may develop. The incubation period is usually 5–19 days but can last as long as 28 days.

■ ■DIAGNOSIS Previously, the most widely used serologic test for diagnosing chlamyd ial infections was the genus-specific CF test, in which assay of paired serum specimens often shows fourfold or greater increases in antibody titer. The CF test remains useful, but the gold standard of serologic tests is now the MIF test, which is not widely available (see section on diagnosis of C. trachomatis genital infection, above). Any antibody titer above 1:16 is considered significant evidence of exposure to chla mydiae, and a fourfold titer rise in paired sera in combination with a clinically compatible syndrome can be used to diagnose psittacosis. Some commercially available serologic tests based on measurement of antibodies to LPS can be useful when the clinical diagnosis is consis tent with bird exposure; however, since these tests are reactive for all chlamydiae (i.e., all chlamydiae contain LPS), caution must be used in their interpretation. NAATs from respiratory samples are highly sensi tive and specific but are not widely available in laboratories. C. psittaci is now considered a biohazard category B biothreat agent and has been

associated with laboratory-acquired infections.

TREATMENT Psittacosis The antibiotic of choice is doxycycline; the dosage for adults is 100 mg twice a day, continued for 10–21 days; it is unclear if lon ger courses prevent relapse. Severely ill patients may need intra venous doxycycline and cardiovascular and respiratory support. Tetracycline (500 mg four times a day by mouth) and azithromycin 250–500 mg by mouth daily for 7 days are alternative therapies. Erythromycin (500 mg four times a day by mouth) appears to be inferior to other agents in animal models. PART 5 Infectious Diseases C. PNEUMONIAE INFECTIONS C. pneumoniae is a common cause of human respiratory diseases, such as pneumonia and bronchitis. This organism reportedly accounts for as many as 10% of cases of community-acquired pneumonia, but more typically 1–2%. PCR is the preferred method for diagnosis of acute infections. Serologic studies have linked C. pneumoniae to atheroscle rosis; isolation and PCR detection in cardiovascular tissues have also been reported. These findings suggest an expanded range of diseases and syndromes for C. pneumoniae. Large-scale case–cohort studies have demonstrated some association of C. pneumoniae with lung can cer, as evaluated by serology. ■ ■EPIDEMIOLOGY Primary infection occurs mainly in school-aged children and reinfec tion in adults. Seroprevalence rates of 40–70% show that C. pneu moniae is widespread in both industrialized and developing countries. Seropositivity usually is first detected at school age, and rates generally increase by ~10% per decade. About 50% of individuals have detectable antibody at 30 years of age, and most have detectable antibody by the eighth decade of life. Although, as mentioned, serologic evidence sug gests that C. pneumoniae may be associated with up to 10% of cases of community-acquired pneumonia, most of this evidence is based not on paired serum samples but rather on a single high IgG titer. Some doubt exists about the true prevalence and etiologic role of C. pneumoniae in atypical pneumonia, especially since reports of cross-reactivity have raised questions about the specificity of serology when only a single serum sample is used for diagnosis. ■ ■PATHOGENESIS Little is known about the pathogenesis of C. pneumoniae infection. It begins in the upper respiratory tract and may persist as a prolonged asymptomatic condition of the upper respiratory mucosal surfaces. However, evidence of replication within vascular endothelium and synovial membranes of joints shows that, in at least some individuals, the organism is transported to distant sites, perhaps within macro phages. A C. pneumoniae outer-membrane protein may induce host

immune responses whose cross-reactivity with human proteins results in an autoimmune reaction. The role of C. pneumoniae in the etiology of atherosclerosis has been discussed since 1988, when Finnish researchers presented serologic evidence of an association of this organism with coronary heart disease and acute myocardial infarction. Subsequently, the organism was identified in atherosclerotic lesions by culture, PCR, immunohistochemistry, and transmission electron microscopy; how ever, discrepant study results (including those of animal studies) and failure of large-scale treatment studies have raised doubts as to the etiologic role of C. pneumoniae in atherosclerosis. Epidemiologic studies have demonstrated an association between serologic evi dence of C. pneumoniae infection and atherosclerotic disease of the coronary and other arteries. In addition, C. pneumoniae has been identified in atherosclerotic plaques by electron microscopy, DNA hybridization, and immunocytochemistry. The organism has been recovered in culture from atheromatous plaques—a result indicating the presence of viable replicating bacteria in vessels. Evidence from animal models supports the hypothesis that C. pneumoniae infection of the upper respiratory tract is followed by recovery of the organism from atheromatous lesions in the aorta and that the infection acceler ates the process of atherosclerosis, especially in

hypercholesterolemic animals. Antimicrobial treatment of the infected animals reverses the increased risk of atherosclerosis. In humans, two small trials in patients with unstable angina or recent myocardial infarction sug gested that antibiotics reduce the likelihood of subsequent cardiac events. However, larger-scale trials have not documented an effect of various antichlamydial regimens on the risk of these events. ■ ■CLINICAL MANIFESTATIONS C. pneumoniae was first reported as the etiologic agent of mild atypi cal pneumonia in military recruits and college students. The clinical spectrum of C. pneumoniae infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonitis, primarily in young adults. The clinical manifestations of primary infection appear to be more severe and prolonged than those of reinfection. The pneumonitis of C. pneu moniae pneumonia resembles that of Mycoplasma pneumonia in that leukocytosis is frequently lacking and patients often have prominent antecedent upper respiratory tract symptoms, fever, nonproductive cough, mild to moderate illness, minimal findings on chest ausculta tion, and small segmental infiltrates on chest x-ray. In elderly patients, pneumonia due to C. pneumoniae can be especially severe and may necessitate hospitalization and respiratory support. Chronic infection with C. pneumoniae has been reported among patients with chronic obstructive pulmonary disease and may play a role in the natural history of asthma, including exacerbations. The clinical symptoms of respiratory infections caused by C. pneumoniae are nonspecific and do not differ from those caused by other agents of atypical pneumonia, such as Mycoplasma pneumoniae. ■ ■DIAGNOSIS PCR amplification of respiratory secretions is the preferred method of diagnosis; several commercial assays are available. Serology and culture can be used to diagnose C. pneumoniae infection. Serology was the traditional diagnostic method. Serology is not FDA approved because of its poor predictive value and is not routinely used clinically. Cell cul ture, which can perform similarly to PCR and allows for antimicrobial susceptibility testing, is seldom used as most clinical laboratories are not equipped to culture Chlamydia spp. The organism is very difficult to grow in tissue cultures but has been cultivated in HeLa cells, HEp-2 cells, and HL cells. Previously, the gold standard serologic test was the MIF test (see section on diagnosis of C. trachomatis genital infection, above). Any antibody titer >1:16 is considered significant evidence of exposure to chlamydiae. According to a CDC-sponsored expert work ing group, the diagnosis of acute C. pneumoniae infection requires demonstration of a fourfold rise in titer in paired serum samples. There are no official recommendations for diagnosis of chronic infections, although many research studies have used high titers of IgA as an indicator. The older CF tests and EIAs for LPS are not recommended,

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Revision #1
Created 2026-01-06 16:33:24 UTC by Omar Ayman
Updated 2026-01-06 16:33:24 UTC by Omar Ayman