NGU is diagnosed by documentation of a leukocytic urethral exudate and by exclusion of gonorrhea by Gram's staining or culture. *C. trachomatis* urethritis is generally less severe than gonococcal 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 of the urethra.

At least one-third of male patients with *C. trachomatis* urethral infection have no evident signs or symptoms of urethritis. The availability of NAATs for first-void urine specimens has facilitated broader-based testing for asymptomatic infection in male patients. As a result, asymptomatic chlamydial urethritis 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 leukocytes 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. To differentiate between true urethritis and functional symptoms in symptomatic patients or to make a presumptive diagnosis of *C. trachomatis* infection in high-risk but asymptomatic men (e.g., male patients in STD clinics, sex partners of women with nongonococcal salpingitis or mucopurulent cervicitis, fathers of children with inclusion conjunctivitis), the examination of an endourethral specimen for increased leukocytes is useful if specific diagnostic tests for chlamydiae are not available. Alternatively, urethritis can be assayed noninvasively by examination of a first-void 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, as described below (see "Detection Methods").

EPIDIDYMITIS Chlamydial urethritis may be followed by acute epididymitis, 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 infection and/or instrumentation procedures. It is estimated that 50–70% of cases of acute epididymitis are caused by *C. trachomatis*. The condition usually 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 antibiotics on an outpatient basis or severe enough to require hospitalization and parenteral therapy. Testicular torsion should be excluded promptly by radionuclide scan, Doppler flow study, 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 (e.g., tuberculosis) should be excluded when a patient with unilateral intrascrotal pain and swelling does not respond to appropriate antimicrobial 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 and is thought to be the most common type of peripheral inflammatory arthritis in young men. *C. trachomatis* has been recovered from the urethra of 16–44% of patients with reactive arthritis and from 69% of men who have 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 EBs 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*. Since >80% of affected patients have the HLA-B27 phenotype and since other mucosal infections produce an identical syndrome, chlamydial infection is thought to initiate an aberrant hyperactive 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 EBs 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 documented 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 anal intercourse. In these infections, rectal involvement is initially characterized by severe anorectal pain, a bloody mucopurulent discharge, and tenesmus. Oculogenital serovars D–K and LGV serovars L_1, L_2, and L_3 have been found to cause proctitis. The LGV serovars are far more invasive and cause much more severely symptomatic disease, including severe ulcerative proctocolitis that can be clinically confused with HSV proctitis. 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 are positive for HIV infection.

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 culture or 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 reportedly more sensitive than culture for diagnosis and are also specific.

MUCOPURULENT CERVICITIS Although many women with chlamydial infections of the cervix have no symptoms, almost half generally 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 Papanicolaou smear shows increased numbers of neutrophils as well as a characteristic pattern of mononuclear inflammatory cells including plasma cells, transformed lymphocytes, and histiocytes. Cervical biopsy shows a predominantly mononuclear cell infiltrate of