



Mindful
Continuing Education

STDs Update: Part Two



Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include dysuria; urethral pruritis; and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present in persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis and, less commonly, prostatitis (470–474). If point-of-care diagnostic tools (e.g., Gram, methylene blue [MB] or gentian violet [GV] stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended to prevent complications, re-infection, and transmission because a specific diagnosis might improve treatment compliance, delivery of risk reduction interventions, and partner notification. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for the detection of *C. trachomatis* and *N. gonorrhoeae*, and urine is the preferred specimen in males (394). NAAT-based tests for the diagnosis of *T. vaginalis* in men have not been cleared by FDA; however, some laboratories have performed the CLIA-compliant validation studies (475) needed to provide such testing.

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID)

TABLE 1. Oral desensitization protocol for persons with a positive skin test*

| Penicillin V suspension dose [†] | Amount [§] (units/mL) | mL | Units | Cumulative dose (units) |
|---|--------------------------------|-----|---------|-------------------------|
| 1 | 1,000 | 0.1 | 100 | 100 |
| 2 | 1,000 | 0.2 | 200 | 300 |
| 3 | 1,000 | 0.4 | 400 | 700 |
| 4 | 1,000 | 0.8 | 800 | 1,500 |
| 5 | 1,000 | 1.6 | 1,600 | 3,100 |
| 6 | 1,000 | 3.2 | 3,200 | 6,300 |
| 7 | 1,000 | 6.4 | 6,400 | 12,700 |
| 8 | 10,000 | 1.2 | 12,000 | 24,700 |
| 9 | 10,000 | 2.4 | 24,000 | 48,700 |
| 10 | 10,000 | 4.8 | 48,000 | 96,700 |
| 11 | 80,000 | 1.0 | 80,000 | 176,700 |
| 12 | 80,000 | 2.0 | 160,000 | 336,700 |
| 13 | 80,000 | 4.0 | 320,000 | 656,700 |
| 14 | 80,000 | 8.0 | 640,000 | 1,296,700 |

Source: Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985;312:1229–32.

* Observation period was 30 minutes before parenteral administration of penicillin.

[†] Interval between doses, 15–30 minutes; elapsed time, 4–8 hours; cumulative dose, 1.3 million units.

[§] The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

or MB/GV purple intracellular diplococci on urethral smear is indicative of presumed gonorrhea infection, which is frequently accompanied by chlamydial infection. NGU, which is diagnosed when microscopy of urethral secretions indicates inflammation without GNID or MB/GV purple intracellular diplococci, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men (476). Documentation of chlamydial infection as the etiology of NGU is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially in female partners. Complications of *C. trachomatis*-associated NGU among males include epididymitis, prostatitis, and reactive arthritis.

M. genitalium, which can be sexually transmitted, is associated with symptoms of urethritis as well as urethral inflammation and accounts for 15%–25% of NGU cases in the United States (470–473). However, FDA-cleared diagnostic tests for *M. genitalium* are not available.

T. vaginalis can cause NGU in heterosexual men, but the prevalence varies substantially by region of the United States and within specific subpopulations. In some instances, NGU can be acquired by fellatio (i.e., oral penile contact), sometimes because of specific pathogens such as HSV, Epstein Barr Virus, and adenovirus (476); data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent. Diagnostic

and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., contact with trichomoniasis, urethral lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to recommended therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (476). The importance of NGU not caused by defined pathogens is uncertain; neither complications (e.g., urethral stricture and epididymitis) nor adverse outcomes in sex partners have been identified in these cases.

Diagnostic Considerations

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if point-of-care diagnostic tests (e.g., Gram, MB or GV, or Gram stain microscopy) are not available, all men should be tested by NAAT and treated with drug regimens effective against both gonorrhea and chlamydia.

In the setting of compatible symptoms, urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucoid, mucopurulent, or purulent discharge on examination.
- Gram stain of urethral secretions demonstrating ≥ 2 WBC per oil immersion field (477). The Gram stain is a point-of-care diagnostic test for evaluating urethritis that is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. MB/GV stain of urethral secretions is an alternative point-of-care diagnostic test with performance characteristics similar to Gram stain; thus, the cutoff number for WBC per oil immersion field should be the same (478). Presumed gonococcal infection is established by documenting the presence of WBC containing GNID in Gram stain or intracellular purple diplococci in MB/GV smears; men should be presumptively treated and managed accordingly for gonorrhea (GC) infection (see Gonococcal Infections).
- Positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥ 10 WBC per high power field.

In settings where Gram stain or MB/GV smear is available, men who meet criteria for urethritis (microscopy of urethral secretions with ≥ 2 WBC per oil immersion field and no intracellular gram negative or purple diplococci) should receive NAAT testing for *C. trachomatis* and *N. gonorrhoeae* and can be managed as recommended (see Nongonococcal Urethritis). Men evaluated in settings in which Gram stain or MB/GV smear is not available (i.e., gonococcal infection cannot be ruled out at the point of care) who meet at least one criterion for urethritis (i.e., urethral discharge, positive LE test on first

void urine, or microscopic exam of first void urine sediment with ≥ 10 WBC per hfp) should be tested by NAAT and treated with regimens effective against gonorrhea and chlamydia.

If symptoms are present but no evidence of urethral inflammation is present, NAAT testing for *C. trachomatis* and *N. gonorrhoeae* might identify infections (479). If the results demonstrate infection with these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these clinical criteria are present, empiric treatment of symptomatic men is recommended only for those men at high risk for infection who are unlikely to return for a follow-up evaluation or test results. Such men should be treated with drug regimens effective against gonorrhea and chlamydia.

Nongonococcal Urethritis

Diagnostic Considerations

NGU is a nonspecific diagnosis that can have many infectious etiologies. NGU is confirmed in symptomatic men when staining of urethral secretions indicates inflammation without Gram negative or purple diplococci. All men who have confirmed NGU should be tested for chlamydia and gonorrhea even if point-of-care tests are negative for evidence of GC. NAATs for chlamydia and gonorrhea are recommended because of their high sensitivity and specificity; a specific diagnosis can potentially reduce complications, re-infection, and transmission (394). Testing for *T. vaginalis* should be considered in areas or populations of high prevalence.

Treatment

Presumptive treatment should be initiated at the time of NGU diagnosis. Azithromycin and doxycycline are highly effective for chlamydial urethritis. NGU associated with *M. genitalium* currently responds better to azithromycin than doxycycline, although azithromycin efficacy might be declining (See *Mycoplasma genitalium*).

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

As a directly observed treatment, single-dose regimens might be associated with higher rates of compliance over other regimens. To maximize compliance with recommended therapies, medications should be dispensed onsite in the clinic, and regardless of the number of doses involved in the regimen, the first should be directly observed.

Other Management Considerations

To minimize transmission and reinfection, men treated for NGU should be instructed to abstain from sexual intercourse until they and their partner(s) have been adequately treated (i.e., for 7 days after single-dose therapy or until completion of a 7-day regimen and symptoms resolved). Men who receive a diagnosis of NGU should be tested for HIV and syphilis.

Follow-Up

Men should be provided results of the testing obtained as part of the NGU evaluation, and those with a specific diagnosis of chlamydia, gonorrhea, or trichomonas should be offered partner services and instructed to return 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (480,481) (see Chlamydia, Follow-Up and Gonorrhea, Follow-Up).

If symptoms persist or recur after completion of therapy, men should be instructed to return for re-evaluation. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for retreatment. Providers should be alert to the possible diagnosis of chronic prostatitis/chronic pelvic pain syndrome in men experiencing persistent perineal, penile, or pelvic pain or discomfort, voiding symptoms, pain during or after ejaculation, or new-onset premature ejaculation lasting for >3 months. Men with persistent pain should be referred to a urologist.

Management of Sex Partners

All sex partners of men with NGU within the preceding 60 days should be referred for evaluation, testing, and presumptive treatment with a drug regimen effective against chlamydia. EPT is an alternative approach to treating female partners for CT in the absence of signs and symptoms of PID (95). If *N. gonorrhoea* or *T. vaginalis* is documented, all partners should be evaluated and treated according to the management section for their respective pathogen. To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partner(s) are adequately treated.

Persistent and Recurrent NGU

The objective diagnosis of persistent or recurrent NGU should be made before considering additional antimicrobial

therapy. In men who have persistent symptoms after treatment without objective signs of urethral inflammation, the value of extending the duration of antimicrobials has not been demonstrated. Men who have persistent or recurrent NGU can be retreated with the initial regimen if they did not comply with the treatment regimen or were re-exposed to an untreated sex partner.

Recent studies have shown that the most common cause of persistent or recurrent NGU is *M. genitalium*, especially following doxycycline therapy (277,278). Azithromycin 1 g orally in a single dose should be administered to men initially treated with doxycycline. Certain observational studies have shown that moxifloxacin 400 mg orally once daily for 7 days is highly effective against *M. genitalium*. Therefore, men who fail a regimen of azithromycin should be retreated with moxifloxacin 400 mg orally once daily for 7 days. Higher doses of azithromycin have not been found to be effective for *M. genitalium* in cases of azithromycin failure (280).

T. vaginalis is also known to cause urethritis in men who have sex with women. Although no NAAT for *T. vaginalis* detection in men has been FDA-cleared in the United States, several large reference laboratories have performed the necessary CLIA validation of a urine-based *T. vaginalis* NAAT for men for clinical use. Trichomonas NAAT testing is more sensitive than culture (475). In areas where *T. vaginalis* is prevalent, men who have sex with women and have persistent or recurrent urethritis should be presumptively treated with metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose; their partners should be referred for evaluation and appropriate treatment. Persons with persistent or recurrent NGU after presumptive treatment for *M. genitalium* or *T. vaginalis* should be referred to a urologist.

Special Considerations

HIV Infection

NGU might facilitate HIV transmission. Persons with NGU and HIV should receive the same treatment regimen as those who are HIV negative.

Cervicitis

Two major diagnostic signs characterize cervicitis: 1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis) and 2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic, but some women complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g.,

after sexual intercourse). A finding of leukorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. In the absence of the major diagnostic signs of inflammatory vaginitis, leukorrhea might be a sensitive indicator of cervical inflammation with a high negative predictive value (i.e., cervicitis is unlikely in the absence of leukorrhea) (482,483). The criterion of using an increased number of WBCs on endocervical Gram stain in the diagnosis of cervicitis has not been standardized and therefore is not helpful. In addition, it has a low positive-predictive value (PPV) for infection with *C. trachomatis* and *N. gonorrhoeae* and is not available in most clinical settings. Finally, although the presence of gram negative intracellular diplococci on Gram stain of endocervical fluid may be specific for the diagnosis of gonococcal cervical infection when evaluated by an experienced laboratorian, it is not a sensitive indicator of infection.

Etiology

When an etiologic organism is isolated in the presence of cervicitis, it is typically *C. trachomatis* or *N. gonorrhoeae*. Cervicitis also can accompany trichomoniasis and genital herpes (especially primary HSV-2 infection). However, in most cases of cervicitis, no organism is isolated, especially in women at relatively low risk for recent acquisition of these STDs (e.g., women aged >30 years) (484). Limited data indicate that infection with *M. genitalium* or BV and frequent douching might cause cervicitis (257–259,261,265,485–487). For reasons that are unclear, cervicitis can persist despite repeated courses of antimicrobial therapy. Because most persistent cases of cervicitis are not caused by recurrent or reinfection with *C. trachomatis* or *N. gonorrhoeae*, other factors (e.g., persistent abnormality of vaginal flora, douching [or exposure to other types of chemical irritants], or idiopathic inflammation in the zone of ectopy) might be involved.

Diagnostic Considerations

Because cervicitis might be a sign of upper-genital-tract infection (endometritis), women with a new episode of cervicitis should be assessed for signs of PID and should be tested for *C. trachomatis* and for *N. gonorrhoeae* with NAAT; such testing can be performed on either vaginal, cervical, or urine samples (394) (see Chlamydia and Gonorrhea Diagnostic Considerations). Women with cervicitis also should be evaluated for the presence of BV and trichomoniasis, and if these are detected, they should be treated. Because the sensitivity of microscopy to detect *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative microscopy for trichomonads should receive further testing (i.e., culture, NAAT or other FDA approved

diagnostic test) (see Trichomoniasis, Diagnosis). A finding of >10 WBC per high power field in vaginal fluid, in the absence of trichomoniasis, might indicate endocervical inflammation caused specifically by *C. trachomatis* or *N. gonorrhoeae* (488,489). Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., PCR, culture or serologic testing) for HSV-2 is unknown. FDA-cleared diagnostic tests for *M. genitalium* are not available.

Treatment

Several factors should affect the decision to provide presumptive therapy for cervicitis. Presumptive treatment with antimicrobials for *C. trachomatis* and *N. gonorrhoeae* should be provided for women at increased risk (e.g., those aged <25 years and those with a new sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection), especially if follow-up cannot be ensured or if testing with NAAT is not possible. Trichomoniasis and BV should also be treated if detected (see Bacterial Vaginosis and Trichomoniasis). For women at lower risk of STDs, deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and NAATs for *C. trachomatis* and *N. gonorrhoeae* are negative, a follow-up visit to see if the cervicitis has resolved can be considered.

Recommended Regimens for Presumptive Treatment*

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

*Consider concurrent treatment for gonococcal infection if patient is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high.

Other Considerations

To minimize transmission and reinfection, women treated for cervicitis should be instructed to abstain from sexual intercourse until they and their partner(s) have been adequately treated (i.e., for 7 days after single-dose therapy or until completion of a 7-day regimen) and symptoms have resolved. Women who receive a diagnosis of cervicitis should be tested for HIV and syphilis.

Follow-Up

Women receiving treatment should return to their provider for a follow-up visit, allowing the provider to determine whether cervicitis has resolved. For women who are not treated, a follow-up visit gives providers an opportunity to communicate results of tests obtained as part of the cervicitis evaluation. Additional follow-up should be conducted as recommended for the infections identified. Women with a

specific diagnosis of chlamydia, gonorrhea, or trichomonas should be offered partner services and instructed to return in 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (480). If symptoms persist or recur, women should be instructed to return for re-evaluation.

Management of Sex Partners

Management of sex partners of women treated for cervicitis should be appropriate for the specific STD identified or suspected. All sex partners in the past 60 days should be referred for evaluation, testing, and presumptive treatment if chlamydia, gonorrhea, or trichomoniasis was identified or suspected in the women with cervicitis. EPT or other effective partner referral strategies (see Partner Services) are alternative approaches to treating male partners of women who have chlamydia or gonococcal infection (93–95). To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partner(s) are adequately treated.

Persistent or Recurrent Cervicitis

Women with persistent or recurrent cervicitis despite having been treated should be reevaluated for possible re-exposure or treatment failure to gonorrhea or chlamydia. If relapse and/or reinfection with a specific STD have been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined; in addition, the utility of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis remains unknown. The etiology of persistent cervicitis including the potential role of *M. genitalium* (490) is unclear. *M. genitalium* might be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which re-exposure to an infected partner or medical nonadherence is unlikely. In settings with validated assays, women with persistent cervicitis could be tested for *M. genitalium* with the decision to treat with moxifloxacin based on results of diagnostic testing (491). In treated women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered.

Special Considerations

HIV Infection

Women with cervicitis and HIV infection should receive the same treatment regimen as those who are HIV negative. Cervicitis increases cervical HIV shedding. Treatment of cervicitis in women with HIV infection reduces HIV shedding from the cervix and might reduce HIV transmission to susceptible sex partners (492–496).

Pregnancy

Diagnosis and treatment of cervicitis in pregnant women does not differ from that in women that are not pregnant. For more information, see Cervicitis, sections on Diagnostic Considerations and Treatment.

Chlamydial Infections

Chlamydial Infections in Adolescents and Adults

Chlamydial infection is the most frequently reported infectious disease in the United States, and prevalence is highest in persons aged ≤ 24 years (118). Several sequelae can result from *C. trachomatis* infection in women, the most serious of which include PID, ectopic pregnancy, and infertility. Some women who receive a diagnosis of uncomplicated cervical infection already have subclinical upper-reproductive-tract infection.

Asymptomatic infection is common among both men and women. To detect chlamydial infections, health-care providers frequently rely on screening tests. Annual screening of all sexually active women aged < 25 years is recommended, as is screening of older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection (108). Although CT incidence might be higher in some women aged ≥ 25 years in some communities, overall the largest burden of infection is among women aged < 25 years.

Chlamydia screening programs have been demonstrated to reduce the rates of PID in women (497,498). Although evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men because of several factors (e.g., feasibility, efficacy, and cost-effectiveness), the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) or in populations with high burden of infection (e.g., MSM) (108,121). Among women, the primary focus of chlamydia screening efforts should be to detect chlamydia, prevent complications, and test and treat their partners, whereas targeted chlamydia screening in men should only be considered when resources permit, prevalence is high, and such screening does not hinder chlamydia screening efforts in women (499,500). More frequent screening for some women (e.g., adolescents) or certain men (e.g., MSM) might be indicated.

Diagnostic Considerations

C. trachomatis urogenital infection can be diagnosed in women by testing first-catch urine or collecting swab specimens from the endocervix or vagina. Diagnosis of *C. trachomatis* urethral infection in men can be made by testing a urethral swab or first-catch urine specimen. NAATs are the most sensitive tests for these specimens and therefore are recommended for detecting *C. trachomatis* infection (394). NAATs that are FDA-cleared for use with vaginal swab specimens can be collected by a provider or self-collected in a clinical setting. Self-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs (501,502), and women find this screening strategy highly acceptable (503,504). Optimal urogenital specimen types for chlamydia screening using NAAT include first catch-urine (men) and vaginal swabs (women) (394). Rectal and oropharyngeal *C. trachomatis* infection in persons engaging in receptive anal or oral intercourse can be diagnosed by testing at the anatomic site of exposure. NAATs are not FDA-cleared for use with rectal or oropharyngeal swab specimens. However, NAATs have been demonstrated to have improved sensitivity and specificity compared with culture for the detection of *C. trachomatis* at rectal sites (505–507) and at oropharyngeal sites among men (505–508). Some laboratories have established CLIA-defined performance specifications when evaluating rectal and oropharyngeal swab specimens for *C. trachomatis*, thereby allowing results to be used for clinical management. Most persons with *C. trachomatis* detected at oropharyngeal sites do not have oropharyngeal symptoms. However, when gonorrhea testing is performed at the oropharyngeal site, chlamydia test results might be reported as well because some NAATs detect both bacteria from a single specimen. Data indicate that performance of NAATs on self-collected rectal swabs is comparable to clinician-collected rectal swabs, and this specimen collection strategy for rectal *C. trachomatis* screening is highly acceptable (509–511). Self-collected rectal swabs are a reasonable alternative to clinician-collected rectal swabs for *C. trachomatis* screening by NAAT, especially when clinicians are not available or when self collection is preferred over clinician collection. Previous evidence suggests that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT testing, although test sensitivity using these specimens might be lower than that associated with use of cervical or vaginal swab specimens (512); regardless, certain NAATs have been FDA-cleared for use on liquid-based cytology specimens.

Treatment

Treating persons infected with *C. trachomatis* prevents adverse reproductive health complications and continued sexual transmission, and treating their sex partners can prevent reinfection and infection of other partners. Treating pregnant women usually prevents transmission of *C. trachomatis* to neonates during birth. Chlamydia treatment should be provided promptly for all persons testing positive for infection; treatment delays have been associated with complications (e.g., PID) in a limited proportion of women (513).

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

A meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of urogenital chlamydial infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively (514). These studies were conducted primarily in populations with urethral and cervical infection in which follow-up was encouraged, adherence to a 7-day regimen was effective, and culture or EIA (rather than the more sensitive NAAT) was used for determining microbiological outcome. More recent retrospective studies have raised concern about the efficacy of azithromycin for rectal *C. trachomatis* infection (515,516), however, these studies have limitations, and prospective clinical trials comparing azithromycin versus doxycycline regimens for rectal *C. trachomatis* infection are needed.

Although the clinical significance of oropharyngeal *C. trachomatis* infection is unclear and routine oropharyngeal screening for CT is not recommended, available evidence suggests oropharyngeal *C. trachomatis* can be sexually transmitted to genital sites (152,517); therefore, detection of *C. trachomatis* from an oropharyngeal specimen should be treated with azithromycin or doxycycline. The efficacy of alternative antimicrobial regimens in resolving oropharyngeal chlamydia remains unknown.

In a double-blinded randomized control trial, a doxycycline delayed-release 200 mg tablet administered daily for 7 days was as effective as generic doxycycline 100 mg twice daily for 7 days for treatment of urogenital *C. trachomatis* infection in men and women and had a lower frequency of gastrointestinal side effects. However, this regimen is more costly than those that involve multiple daily doses (518). Delayed-release doxycycline (Doryx) 200 mg daily for 7 days might be an alternative regimen to the doxycycline 100 mg twice daily for 7 days for treatment of urogenital *C. trachomatis* infection. Erythromycin might be less efficacious than either azithromycin or doxycycline, mainly because of the frequent occurrence of gastrointestinal side effects that can lead to nonadherence with treatment. Levofloxacin and ofloxacin are effective treatment alternatives, but they are more expensive and offer no advantage in the dosage regimen. Other quinolones either are not reliably effective against chlamydial infection or have not been evaluated adequately.

Other Management Considerations

To maximize adherence with recommended therapies, onsite, directly observed single-dose therapy with azithromycin should always be available for persons for whom adherence with multidose therapy is a concern. In addition, for multidose regimens, the first dose should be dispensed on site and directly observed. To minimize disease transmission to sex partners, persons treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen and resolution of symptoms if present. To minimize risk for reinfection, patients also should be instructed to abstain from sexual intercourse until all of their sex partners are treated. Persons who receive a diagnosis of chlamydia should be tested for HIV, GC, and syphilis.

Follow-Up

Test-of-cure to detect therapeutic failure (i.e., repeat testing 3–4 weeks after completing therapy) is not advised for persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. Moreover, the use of chlamydial NAATs at <3 weeks after completion of therapy is not recommended because the continued presence of nonviable organisms (394,395,519) can lead to false-positive results.

A high prevalence of *C. trachomatis* infection has been observed in women and men who were treated for chlamydial infection during the preceding several months (480,481,520–522). Most post-treatment infections do not result from treatment failure, but rather from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a

new infected partner, indicating a need for improved education and treatment of sex partners. Repeat infections confer an elevated risk for PID and other complications in women. Men and women who have been treated for chlamydia should be retested approximately 3 months after treatment, regardless of whether they believe that their sex partners were treated (480,481). If retesting at 3 months is not possible, clinicians should retest whenever persons next present for medical care in the 12-month period following initial treatment.

Management of Sex Partners

Sexual partners should be referred for evaluation, testing, and presumptive treatment if they had sexual contact with the partner during the 60 days preceding the patient's onset of symptoms or chlamydia diagnosis. Although the exposure intervals defined for the identification of at-risk sex partners are based on limited data, the most recent sex partner should be evaluated and treated, even if the time of the last sexual contact was >60 days before symptom onset or diagnosis.

Among heterosexual patients, if health department partner management strategies (e.g., disease intervention specialists) are impractical or not available for persons with chlamydia and a provider is concerned that sex partners are unable to promptly access evaluation and treatment services, EPT should be considered as permitted by law (see Partner Services). Compared with standard patient referral of partners, this approach to therapy, which involves delivering the medication itself or a prescription, has been associated with decreased rates of persistent or recurrent chlamydia (93–95). Providers should also provide patients with written educational materials to give to their partner(s) about chlamydia in general, to include notification that partner(s) have been exposed and information about the importance of treatment. These materials also should inform partners about potential therapy-related allergies and adverse effects, along with symptoms suggestive of complications (e.g., testicular pain in men and pelvic or abdominal pain in women). EPT is not routinely recommended for MSM with chlamydia because of a high risk for coexisting infections (especially undiagnosed HIV) among their partners, and because data are limited regarding the effectiveness of this approach in reducing persistent or recurrent chlamydia among MSM. Having partners accompany patients when they return for treatment is another strategy that has been used to ensure partner treatment (See Partner Services). To avoid reinfection, sex partners should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., for 7 days after a single-dose regimen or after completion of a 7-day regimen) and have resolved any symptoms.

Special Considerations

Pregnancy

Doxycycline is contraindicated in the second and third trimesters of pregnancy. Human data suggest ofloxacin and levofloxacin present a low risk to the fetus during pregnancy, with a potential for toxicity during breastfeeding; however, data from animal studies raise concerns about cartilage damage to neonates (317). Thus, alternative drugs should be used to treat chlamydia in pregnancy. Clinical experience and published studies suggest that azithromycin is safe and effective (523–525). Test-of-cure to document chlamydial eradication (preferably by NAAT) 3–4 weeks after completion of therapy is recommended because severe sequelae can occur in mothers and neonates if the infection persists. In addition, all pregnant women who have chlamydial infection diagnosed should be retested 3 months after treatment. Detection of *C. trachomatis* infection at repeat screening during the third semester is not uncommon in adolescent and young adult women, including in those without *C. trachomatis* detected at the time of initial prenatal screening (526,527). Women aged <25 years and those at increased risk for chlamydia (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection) should be rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant (108).

Recommended Regimens

Azithromycin 1 g orally in a single dose

Alternative Regimens

Amoxicillin 500 mg orally three times a day for 7 days

OR

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin base 250 mg orally four times a day for 14 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 400 mg orally four times a day for 14 days

Because of concerns about chlamydia persistence following exposure to penicillin-class antibiotics that has been demonstrated in animal and in vitro studies, amoxicillin is now considered an alternative therapy for *C. trachomatis* in pregnant women (528,529). The frequent gastrointestinal side effects associated with erythromycin can result in nonadherence with these alternative regimens. The lower dose 14-day erythromycin regimens can be considered if gastrointestinal

tolerance is a concern. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity.

HIV Infection

Persons who have chlamydia and HIV infection should receive the same treatment regimen as those who do not have HIV infection. For more information, see Chlamydia, Treatment.

Chlamydial Infections Among Neonates

Prenatal screening and treatment of pregnant women is the best method for preventing chlamydial infection among neonates. *C. trachomatis* infection of neonates results from perinatal exposure to the mother's infected cervix. Although the efficacy of neonatal ocular prophylaxis with erythromycin ophthalmic ointments to prevent chlamydia ophthalmia is not clear, ocular prophylaxis with these agents prevents gonococcal ophthalmia and therefore should be administered (see Ophthalmia Neonatorum Caused by *N. gonorrhoeae*).

Initial *C. trachomatis* neonatal infection involves the mucous membranes of the eye, oropharynx, urogenital tract, and rectum, although infection might be asymptomatic in these locations. Instead, *C. trachomatis* infection in neonates is most frequently recognized by conjunctivitis that develops 5–12 days after birth. *C. trachomatis* also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. Although *C. trachomatis* has been the most frequent identifiable infectious cause of ophthalmia neonatorum, neonatal chlamydial infections (including ophthalmia and pneumonia) have occurred less frequently since the institution of widespread prenatal screening and treatment of pregnant women.

Ophthalmia Neonatorum Caused by *C. trachomatis*

A chlamydial etiology should be considered for all infants aged ≤30 days that have conjunctivitis, especially if the mother has a history of chlamydia infection. These infants should receive evaluation and appropriate care and treatment.

Diagnostic Considerations

Sensitive and specific methods used to diagnose chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (e.g., direct fluorescence antibody [DFA] tests and NAAT). DFA is the only nonculture FDA-cleared test for the detection of chlamydia from conjunctival swabs; NAATs are not FDA-cleared for the detection of chlamydia from conjunctival swabs, and clinical laboratories must verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid using a dacron-tipped swab or the swab

specified by the manufacturer's test kit; for culture and DFA, specimens must contain conjunctival cells, not exudate alone. Ocular specimens from neonates being evaluated for chlamydial conjunctivitis also should be tested for *N. gonorrhoeae* (see Ophthalmia Neonatorum Caused by *N. gonorrhoeae*).

Treatment of Ophthalmia Neonatorum

| Recommended Regimen |
|---|
| Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days* |

| Alternative Regimen |
|---|
| Azithromycin suspension, 20 mg/kg/day orally, 1 dose daily for 3 days* |
| * An association between oral erythromycin and azithromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged <6 weeks. Infants treated with either of these antimicrobials should be followed for signs and symptoms of IHPS. |

Although data on the use of azithromycin for the treatment of neonatal chlamydia infection are limited, available data suggest a short course of therapy might be effective (530). Topical antibiotic therapy alone is inadequate for treatment for ophthalmia neonatorum caused by chlamydia and is unnecessary when systemic treatment is administered.

Follow-Up

Because the efficacy of erythromycin treatment for ophthalmia neonatorum is approximately 80%, a second course of therapy might be required (531). Data on the efficacy of azithromycin for ophthalmia neonatorum are limited. Therefore, follow-up of infants is recommended to determine whether initial treatment was effective. The possibility of concomitant chlamydial pneumonia should be considered (see Infant Pneumonia Caused by *C. trachomatis*).

Management of Mothers and Their Sex Partners

Mothers of infants who have ophthalmia caused by chlamydia and the sex partners of these women should be evaluated and presumptively treated for chlamydia. For more information, see Chlamydial Infection in Adolescents and Adults.

Infant Pneumonia Caused by *C. trachomatis*

Chlamydia pneumonia in infants typically occurs at 1–3 months and is a subacute pneumonia. Characteristic signs of chlamydial pneumonia in infants include 1) a repetitive staccato cough with tachypnea and 2) hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia (≥ 400 cells/mm³) occurs frequently. Because clinical presentations differ, all infants aged

1–3 months suspected of having pneumonia (especially those whose mothers have a history of chlamydial infection) should be tested for *C. trachomatis* and treated if infected.

Diagnostic Considerations

Specimens for chlamydial testing should be collected from the nasopharynx. Tissue culture is the definitive standard diagnostic test for chlamydial pneumonia. Nonculture tests (e.g., DFA and NAAT) can be used. DFA is the only nonculture FDA-cleared test for the detection of *C. trachomatis* from nasopharyngeal specimens, but DFA of nasopharyngeal specimens has a lower sensitivity and specificity than culture. NAATs are not FDA-cleared for the detection of chlamydia from nasopharyngeal specimens, and clinical laboratories must verify the procedure according to CLIA regulations (394). Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*.

Treatment

Because test results for chlamydia often are not available at the time that initial treatment decisions must be made, treatment for *C. trachomatis* pneumonia must frequently be based on clinical and radiologic findings, age of the infant (i.e., 1–3 months), and risk of chlamydia in the mother (i.e., age <25, multiple partners, and history of chlamydial infection). The results of tests for chlamydial infection assist in the management of an infant's illness.

| Recommended Regimen |
|--|
| Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days |

| Alternative Regimen |
|---|
| Azithromycin 20 mg/kg/day orally, 1 dose daily for 3 days |

Follow-Up

Because the effectiveness of erythromycin in treating pneumonia caused by *C. trachomatis* is approximately 80%, a second course of therapy might be required (532). Data on the effectiveness of azithromycin in treating chlamydial pneumonia are limited. Follow-up of infants is recommended to determine whether the pneumonia has resolved, although some infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later in childhood.

Management of Mothers and Their Sex Partners

Mothers of infants who have chlamydia pneumonia and the sex partners of these women should be evaluated, tested, and

presumptively treated for chlamydia. For more information, see Chlamydial Infection in Adolescents and Adults.

Neonates Born to Mothers Who Have Chlamydial Infection

Neonates born to mothers who have untreated chlamydia are at high risk for infection; however, prophylactic antibiotic treatment is not indicated, as the efficacy of such treatment is unknown. Infants should be monitored to ensure appropriate treatment if symptoms develop.

Chlamydial Infections Among Infants and Children

Sexual abuse must be considered a cause of chlamydial infection in infants and children. However, perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum might persist for 2–3 years (see Sexual Assault or Abuse of Children).

Diagnostic Considerations

NAAT can be used for vaginal and urine specimens from girls (see Sexual Assault or Abuse of Children), although data are insufficient to recommend the use of NAAT in boys. Data also are lacking regarding use of NAAT for specimens from extragenital sites (rectum and pharynx) in boys and girls (394); other nonculture tests (e.g., DFA) are not recommended because of specificity concerns. Culture is still the preferred method for detection of urogenital *C. trachomatis* in boys and at extragenital sites in boys and girls.

Recommended Regimen for Infants and Children Who Weigh <45 kg

Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days
Data are limited on the effectiveness and optimal dose of azithromycin for the treatment of chlamydial infection in infants and children who weigh <45 kg

Recommended Regimen for Children Who Weigh ≥45 kg but Who Are Aged <8 Years

Azithromycin 1 g orally in a single dose

Recommended Regimens for Children Aged ≥8 years

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Other Management Considerations

See Sexual Assault or Abuse of Children.

Follow-Up

A test-of-cure culture (repeat testing after completion of therapy) to detect therapeutic failure ensures treatment effectiveness. Therefore, a culture should be obtained at a follow-up visit approximately 2 weeks after treatment is completed.

Gonococcal Infections

Gonococcal Infections in Adolescents and Adults

In the United States, an estimated 820,000 new *N. gonorrhoeae* infections occur each year (533). Gonorrhea is the second most commonly reported communicable disease (118). Urethral infections caused by *N. gonorrhoeae* among men can produce symptoms that cause them to seek curative treatment soon enough to prevent sequelae, but often not soon enough to prevent transmission to others. Among women, gonococcal infections are commonly asymptomatic or might not produce recognizable symptoms until complications (e.g., PID) have occurred. PID can result in tubal scarring that can lead to infertility and ectopic pregnancy.

Annual screening for *N. gonorrhoeae* infection is recommended for all sexually active women aged <25 years and for older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) (108). Additional risk factors for gonorrhea include inconsistent condom use among persons who are not in mutually monogamous relationships, previous or coexisting sexually transmitted infections, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and might opt to consult local public health authorities for guidance on identifying groups at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. Subgroups of MSM are at high risk for gonorrhea infection and should be screened at sites of exposure (see MSM). Screening for gonorrhea in men and older women who are at low risk for infection is not recommended (108). A recent travel history with sexual contacts outside of the United States should be part of any gonorrhea evaluation.

Diagnostic Considerations

Specific microbiologic diagnosis of infection with *N. gonorrhoeae* should be performed in all persons at risk for or suspected to have gonorrhea; a specific diagnosis can potentially reduce complications, reinfections, and transmission. Culture and NAAT are available for the detection of genitourinary infection with *N. gonorrhoeae* (394); culture requires endocervical (women) or urethral (men) swab specimens. NAAT allows for the widest variety of FDA-cleared specimen types, including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women). However, product inserts for each NAAT manufacturer must be carefully consulted because collection methods and specimen types vary. Culture is available for detection of rectal, oropharyngeal, and conjunctival gonococcal infection, but NAAT is not FDA-cleared for use with these specimens. Some laboratories have met CLIA regulatory requirements and established performance specifications for using NAAT with rectal and oropharyngeal swab specimens that can inform clinical management. Certain NAATs that have been demonstrated to detect commensal *Neisseria* species might have comparable low specificity when testing oropharyngeal specimens for *N. gonorrhoeae* (394). The sensitivity of NAAT for the detection of *N. gonorrhoeae* in urogenital and nongenital anatomic sites is superior to culture, but varies by NAAT type (394,505–508). In cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing because nonculture tests cannot provide antimicrobial susceptibility results. Because *N. gonorrhoeae* has demanding nutritional and environmental growth requirements, optimal recovery rates are achieved when specimens are inoculated directly and when the growth medium is promptly incubated in an increased CO₂ environment (394). Several non-nutritive swab transport systems are available that might maintain gonococcal viability for up to 48 hours in ambient temperatures (534–536).

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of urethral secretions that demonstrates polymorphonuclear leukocytes with intracellular Gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* in symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection in asymptomatic men. Detection of infection using Gram stain of endocervical, pharyngeal, and rectal specimens also is insufficient and is not recommended. MB/GV stain of urethral secretions is an alternative point-of-care diagnostic test with performance characteristics similar to Gram stain. Presumed gonococcal infection is established by documenting the presence of WBC containing intracellular purple diplococci in MB/GV smears.

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobials (537). In 1986, the Gonococcal Isolate Surveillance Project (GISP), a national sentinel surveillance system, was established to monitor trends in antimicrobial susceptibilities of urethral *N. gonorrhoeae* strains in the United States (538). The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations and has evolved because of shifts in antimicrobial resistance patterns. In 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted CDC to cease recommending fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining class of antimicrobials available for treatment of gonorrhea in the United States (539). Reflecting concern about emerging gonococcal resistance, CDC's 2010 STD treatment guidelines recommended dual therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline, even if NAAT for *C. trachomatis* was negative at the time of treatment (1). However, during 2006–2011, the minimum concentrations of cefixime needed to inhibit in vitro growth of the *N. gonorrhoeae* strains circulating in the United States and many other countries increased, suggesting that the effectiveness of cefixime might be waning (118,540). In addition, treatment failures with cefixime or other oral cephalosporins have been reported in Asia (541–544), Europe (545–549), South Africa (550), and Canada (551,552). Ceftriaxone treatment failures for pharyngeal infections have been reported in Australia (553,554), Japan (555), and Europe (556,557). As a result, CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States (540). In addition, U.S. gonococcal strains with elevated MICs to cefixime also are likely to be resistant to tetracyclines but susceptible to azithromycin (540). Consequently, only one regimen, dual treatment with ceftriaxone and azithromycin, is recommended for treatment of gonorrhea in the United States. CDC (<http://www.cdc.gov/std/gisp>) and state health departments can provide the most current information on gonococcal susceptibility.

Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical and Laboratory Standards Institute (CLSI). However, isolates with cefixime or ceftriaxone MICs $\geq 0.5 \mu\text{g/mL}$ are considered to have decreased susceptibility (558). In the United States, the proportion of isolates in GISP demonstrating decreased susceptibility to ceftriaxone or cefixime has remained low; during 2013, no isolates with decreased susceptibility (MIC $\geq 0.5 \mu\text{g/mL}$) to ceftriaxone or cefixime were identified (118). Because increasing MICs

might predict the emergence of resistance, GISP established lower cephalosporin MIC breakpoints than those set by CLSI to provide greater sensitivity in detecting declining gonococcal susceptibility for surveillance purposes. The percentage of isolates with cefixime MICs $\geq 0.25 \mu\text{g/mL}$ increased from 0.1% in 2006 to 1.4% in 2011 (118,540), and declined to 0.4% in 2013 (118). The percentage of isolates with ceftriaxone MICs $\geq 0.125 \mu\text{g/mL}$ increased from $<0.1\%$ in 2006 to 0.4% in 2011 and decreased to 0.05% in 2013. Isolates with high-level cefixime and ceftriaxone MICs (cefixime MICs 1.5–8 $\mu\text{g/mL}$ and ceftriaxone MICs 1.5–4 $\mu\text{g/mL}$) have been identified in Japan (555), France (549), and Spain (559,560). Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue; state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (537). Although approximately 3% of all U.S. men who have gonococcal infections are sampled through GISP, surveillance by clinicians also is critical. Clinicians who diagnose *N. gonorrhoeae* infection in a person with suspected cephalosporin treatment failure should perform culture and antimicrobial susceptibility testing (AST) of relevant clinical specimens, consult an infectious-disease specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities. Isolates should be saved and sent to CDC through local and state public health laboratory mechanisms. Health departments should prioritize notification and culture evaluation for sexual partner(s) of persons with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or persons whose isolates demonstrate decreased susceptibility to cephalosporin.

Dual Therapy for Gonococcal Infections

On the basis of experience with other microbes that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using two antimicrobials with different mechanisms of action (e.g., a cephalosporin plus azithromycin) to improve treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins. Use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among GISP isolates, particularly in strains with elevated cefixime MICs (118,540). In addition, clinical trials have demonstrated the efficacy of azithromycin 1 g for the treatment of uncomplicated urogenital GC (561,562).

Limited data suggest that dual treatment with azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins (563,564). In addition,

persons infected with *N. gonorrhoeae* frequently are coinfecting with *C. trachomatis*; this finding has led to the longstanding recommendation that persons treated for gonococcal infection also be treated with a regimen that is effective against uncomplicated genital *C. trachomatis* infection, further supporting the use of dual therapy that includes azithromycin (565).

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimen

Ceftriaxone 250 mg IM in a single dose
PLUS
Azithromycin 1 g orally in a single dose

As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation. Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in clinical trials (566,567). No clinical data exist to support use of doses of ceftriaxone $>250 \text{ mg}$.

Single-dose injectable cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and generally effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime (500 mg IM), cefoxitin (2 g IM with probenecid 1 g orally), and cefotaxime (500 mg IM). None of these injectable cephalosporins offer any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain (566,567). Several other antimicrobials are active against *N. gonorrhoeae*, but none have substantial advantages over the recommended regimen, and efficacy data (especially for pharyngeal infection) are limited.

Alternative Regimens

If ceftriaxone is not available:
Cefixime 400 mg orally in a single dose
PLUS
Azithromycin 1 g orally in a single dose

A 400-mg oral dose of cefixime should only be considered as an alternative cephalosporin regimen because it does not provide as high, nor as sustained, bactericidal blood levels as a 250-mg dose of ceftriaxone; further, it demonstrates limited efficacy for treatment of pharyngeal gonorrhea (92.3% cure; 95% confidence interval [CI] = 74.9%–99.1%); in older clinical studies, cefixime cured 97.5% of uncomplicated urogenital and

anorectal gonococcal infections (95% CI = 95.4%–99.8%) (566,567). The increase in the prevalence of isolates obtained through GISP with elevated cefixime MICs might indicate early stages of development of clinically significant gonococcal resistance to cephalosporins. CDC anticipates that rising cefixime MICs soon will result in declining effectiveness of cefixime for the treatment of urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued use of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last antimicrobial known to be highly effective in a single dose for treatment of gonorrhea at all anatomic sites of infection. Other oral cephalosporins (e.g., cefpodoxime and cefuroxime) are not recommended because of inferior efficacy and less favorable pharmacodynamics (566,568).

Because of the prevalence of tetracycline resistance among GISP isolates, particularly those with elevated cefixime MICs (118), the use of azithromycin as the second antimicrobial is preferred. However, in the case of azithromycin allergy, doxycycline (100 mg orally twice a day for 7 days) can be used in place of azithromycin as an alternative second antimicrobial when used in combination with ceftriaxone or cefixime.

In a recent clinical trial, dual treatment of uncomplicated, urogenital gonorrhea with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g was associated with cure rates of 99.5% (lower one-sided 95% CI bound = 97.6%), and dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g cured 100% of cases (lower one-sided 95% CI bound = 98.5%) (569). This trial was not powered to provide reliable estimates of the efficacy of these regimens for treatment of rectal or pharyngeal infection, but both regimens cured the few extragenital infections among study participants. Either of these regimens might be considered as alternative treatment options in the presence of cephalosporin allergy. However, gastrointestinal adverse events might limit their use: 7.7% of patients treated with gemifloxacin plus azithromycin and 3.3% of patients treated with gentamicin plus azithromycin vomited within 1 hour of medication administration, necessitating retreatment with a ceftriaxone and azithromycin.

Spectinomycin, which is useful in persons who cannot tolerate cephalosporins, is expensive, has poor efficacy against pharyngeal infection (51.8%; 95% CI = 38.7%–64.9%) (566), and is not being produced in the United States (570). However, it has been effective in clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections (566). When available, spectinomycin is an effective alternative for the treatment of urogenital and anorectal infection.

Monotherapy with azithromycin 2 g orally as a single dose has been demonstrated to be 99.2% effective against uncomplicated

urogenital gonorrhea (95% CI = 97.3%–99.9%) (567). However, monotherapy is no longer recommended because of concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides, and because several studies have documented azithromycin treatment failures (546,571–574). Strains of *N. gonorrhoeae* circulating in the United States are not adequately susceptible to penicillins, tetracyclines, and older macrolides (e.g., erythromycin), and thus use of these antimicrobials cannot be recommended.

Uncomplicated Gonococcal Infections of the Pharynx

Most gonococcal infections of the pharynx are asymptomatic and can be relatively common in some populations (505,506,575,576). Gonococcal infections of the pharynx are more difficult to eradicate than are infections at urogenital and anorectal sites (551). Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections (566,567). Providers should ask their patients with urogenital or rectal GC about oral sexual exposure; if reported, patients should be treated with a regimen with acceptable efficacy against pharyngeal gonorrhea infection.

Recommended Regimen

| |
|--|
| Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1 g orally in a single dose |
|--|

Other Management Considerations

To maximize adherence with recommended therapies and reduce complications and transmission, medication for gonococcal infection should be provided on site and directly observed. If medications are not available when treatment is indicated, linkage to an STD treatment facility should be provided for same-day treatment. To minimize disease transmission, persons treated for gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). All persons who receive a diagnosis of gonorrhea should be tested for other STDs, including chlamydia, syphilis, and HIV.

Follow-Up

A test-of-cure is not needed for persons who receive a diagnosis of uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens; however, any person with pharyngeal gonorrhea

who is treated with an alternative regimen should return 14 days after treatment for a test-of-cure using either culture or NAAT. If the NAAT is positive, effort should be made to perform a confirmatory culture before retreatment. All positive cultures for test-of-cure should undergo antimicrobial susceptibility testing.

Symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by other organisms (see Urethritis, Cervicitis, and Proctitis sections).

A high prevalence of *N. gonorrhoeae* infection has been observed among men and women previously treated for gonorrhea (86,480,481,577). Rather than signaling treatment failure, most of these infections result from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner, indicating a need for improved patient education and treatment of sex partners. Men or women who have been treated for gonorrhea should be retested 3 months after treatment regardless of whether they believe their sex partners were treated. If retesting at 3 months is not possible, clinicians should retest whenever persons next present for medical care within 12 months following initial treatment.

Management of Sex Partners

Recent sex partners (i.e., persons having sexual contact with the infected patient within the 60 days preceding onset of symptoms or gonorrhea diagnosis) should be referred for evaluation, testing, and presumptive dual treatment. If the patient's last potential sexual exposure was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. To avoid reinfection, sex partners should be instructed to abstain from unprotected sexual intercourse for 7 days after they and their sexual partner(s) have completed treatment and after resolution of symptoms, if present.

For heterosexual men and women with gonorrhea for whom health department partner-management strategies are impractical or unavailable and whose providers are concerned about partners' access to prompt clinical evaluation and treatment, EPT with cefixime 400 mg and azithromycin 1 g can be delivered to the partner by the patient, a disease investigation specialist, or a collaborating pharmacy as permitted by law (see Partner Services). With this approach, provision of medication must be accompanied by written materials (93,95) to educate partners about their exposure to gonorrhea, the importance of therapy, and when to seek clinical evaluation for adverse reactions or complications. Educational materials for female partners should include information about the

importance of seeking medical evaluation for PID (especially if symptomatic); undertreatment of PID in female partners and missed opportunities to diagnose other STDs in women are of concern. EPT should not be considered a routine partner management strategy in MSM with gonorrhea because of a high risk for coexisting infections (especially HIV infection) and because no data exist on efficacy in this population.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Allergic reactions to first-generation cephalosporins occur in <2.5% of persons with a history of penicillin allergy and are uncommon with third-generation cephalosporins (e.g., ceftriaxone and cefixime) (428,430,464). Use of ceftriaxone or cefixime is contraindicated in persons with a history of an IgE-mediated penicillin allergy (e.g., anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis) (428,431). Data are limited regarding alternative regimens for treating gonorrhea among persons who have either a cephalosporin or IgE-mediated penicillin allergy. Potential therapeutic options are dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g (569). Spectinomycin for treatment of urogenital and anorectal gonorrhea can be considered when available. Providers treating persons with cephalosporin or IgE-mediated penicillin allergy should consult an infectious-disease specialist.

Pregnancy

Pregnant women infected with *N. gonorrhoeae* should be treated with dual therapy consisting of ceftriaxone 250 mg in a single IM dose and azithromycin 1 g orally as a single dose. When cephalosporin allergy or other considerations preclude treatment with this regimen and spectinomycin is not available, consultation with an infectious-disease specialist is recommended.

HIV Infection

Persons who have gonorrhea and HIV infection should receive the same treatment regimen as those who are HIV negative. For more information, see appropriate treatment sections under Gonococcal Infections.

Suspected Cephalosporin Treatment Failure

Cephalosporin treatment failure is the persistence of *N. gonorrhoeae* infection despite appropriate cephalosporin treatment and is indicative of infection with cephalosporin-resistant gonorrhea in persons whose partners were adequately treated and whose risk for reinfection is low. Suspected

treatment failure has been reported among persons receiving oral and injectable cephalosporins (541–557,578). Treatment failure should be considered in 1) persons whose symptoms do not resolve within 3–5 days after appropriate treatment and report no sexual contact during the post-treatment follow-up period and 2) persons with a positive test-of-cure (i.e., positive culture ≥ 72 hours or positive NAAT ≥ 7 days after receiving recommended treatment) when no sexual contact is reported during the post-treatment follow-up period (579). Treatment failure should also be considered in persons who have a positive culture on test-of-cure (if obtained) if there is evidence of decreased susceptibility to cephalosporins on antimicrobial susceptibility testing, regardless of whether sexual contact is reported during the post-treatment follow-up period.

Most suspected treatment failures in the United States are likely to be re-infections rather than actual treatment failures (86,480,481,577). However, in cases where reinfection is unlikely and treatment failure is suspected, before retreatment, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing if *N. gonorrhoeae* is isolated. Phenotypic antimicrobial susceptibility testing should be performed using disk diffusion, Etest (BioMérieux, Durham, NC), or agar dilution. Data are limited on the use of DNA amplification and sequencing for detection of genetic mutations associated with gonococcal antimicrobial resistance. All isolates of suspected treatment failures should be sent to CDC for antimicrobial susceptibility testing by agar dilution; local laboratories should store isolates for possible further testing if needed. Testing and/or storage of specimens or isolates should be facilitated by the state or local health department according to local public health protocol.

For persons with suspected cephalosporin treatment failure, the treating clinician should consult an infectious-disease specialist, an STD/HIV Prevention Training Center clinical expert (<http://www.nnptc.org>), the local or state health department STD program, or CDC (telephone: 404-639-8659) for advice on obtaining cultures, antimicrobial susceptibility testing, and treatment. Suspected treatment failure should be reported to CDC through the local or state health department within 24 hours of diagnosis.

Suspected treatment failures first should be retreated routinely with the recommended regimen (ceftriaxone 250 mg IM plus azithromycin 1 g orally), because reinfections are more likely than actual treatment failures. However, in situations with a higher likelihood of treatment failure than reinfection, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing performed before retreatment. Dual treatment with single doses of oral gemifloxacin 320 mg plus

oral azithromycin 2 g or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g can be considered, particularly when isolates are found to have elevated cephalosporin MICs (569). Persons with suspected treatment failure after treatment with the alternative regimen (cefixime and azithromycin) should be treated with ceftriaxone 250 mg as a single IM dose and azithromycin 2 g orally as a single dose. A test-of-cure at relevant clinical sites should be obtained 7–14 days after retreatment; culture is the recommended test, preferably with simultaneous NAAT and antimicrobial susceptibility testing of *N. gonorrhoeae* if isolated. Clinicians should ensure that the patient's sex partners from the preceding 60 days are evaluated promptly with culture and presumptively treated using the same regimen used for the patient.

Gonococcal Conjunctivitis

In the only published study (conducted in 1989) of the treatment of gonococcal conjunctivitis among adults, all 12 study participants responded to a single 1 g IM injection of ceftriaxone (580). On the basis of experience with other microbes that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using two antimicrobials with different mechanisms of action (e.g., a cephalosporin plus azithromycin) to improve treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins. Because gonococcal conjunctivitis is uncommon and data on treatment of gonococcal conjunctivitis in adults are limited, consultation with an infectious-disease specialist should be considered.

Recommended Regimen

| |
|---|
| Ceftriaxone 1 g IM in a single dose PLUS Azithromycin 1 g orally in a single dose |
|---|

Consider one-time lavage of the infected eye with saline solution.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment. For more information, see Gonococcal Infections, Management of Sex Partners.

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI) frequently results in petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis (581). The infection is complicated occasionally by perihepatitis and rarely by endocarditis or meningitis. Some

strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation. If DGI is suspected, NAAT or culture specimens from urogenital and extragenital sites, as applicable, should be collected and processed in addition to specimens from disseminated sites of infection (e.g., skin, synovial fluid, blood, and the CNS). All *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility.

Hospitalization and consultation with an infectious-disease specialist are recommended for initial therapy, especially for persons who might not comply with treatment, have an uncertain diagnosis, or have purulent synovial effusions or other complications. Examination for clinical evidence of endocarditis and meningitis should be performed.

Treatment of Arthritis and Arthritis-Dermatitis Syndrome

| Recommended Regimen |
|---|
| Ceftriaxone 1 g IM or IV every 24 hours PLUS Azithromycin 1 g orally in a single dose |

| Alternative Regimens |
|---|
| Cefotaxime 1 g IV every 8 hours OR Ceftizoxime 1 g IV every 8 hours PLUS Azithromycin 1 g orally in a single dose |

When treating for the arthritis-dermatitis syndrome, the provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days.

Treatment of Gonococcal Meningitis and Endocarditis

| Recommended Regimen |
|--|
| Ceftriaxone 1–2 g IV every 12–24 hours PLUS Azithromycin 1 g orally in a single dose |

No recent studies have been published on the treatment of DGI. The duration of treatment of DGI has not been systematically studied and should be determined in consultation with an infectious-disease specialist. Treatment for DGI should be guided by the results of antimicrobial susceptibility testing. Pending antimicrobial susceptibility results, treatment decisions should be made on the basis of clinical presentation. Therapy for meningitis should be continued with recommended parenteral therapy for

10–14 days. Parenteral antimicrobial therapy for endocarditis should be administered for at least 4 weeks.

Management of Sex Partners

Gonococcal infection frequently is asymptomatic in sex partners of persons who have DGI. Providers should instruct patients to refer partners with whom they have had sexual contact in the past 60 days for evaluation, testing, and presumptive treatment (see Gonococcal Infection, Management of Sex Partners).

Gonococcal Infections Among Neonates

Prenatal screening and treatment of pregnant women is the best method for preventing GC infection among neonates. Gonococcal infection among neonates results from perinatal exposure to the mother's infected cervix. It is usually an acute illness that manifests 2–5 days after birth. The prevalence of infection among infants depends on the prevalence of infection among pregnant women, whether pregnant women are screened and treated for gonorrhea, and whether newborns receive ophthalmia prophylaxis. The most severe manifestations of *N. gonorrhoeae* infection in newborns are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and infection at sites of fetal monitoring.

Ophthalmia Neonatorum Prophylaxis

To prevent gonococcal ophthalmia neonatorum, a prophylactic agent should be instilled into both eyes of all newborn infants; this procedure is required by law in most states. Ocular prophylaxis is warranted because it can prevent sight-threatening gonococcal ophthalmia, has an excellent safety record, is easy to administer, and is inexpensive. The recommended prophylactic regimen prevents gonococcal ophthalmia; however, its efficacy for prevention of chlamydial ophthalmia is less clear, and it does not eliminate nasopharyngeal colonization by *C. trachomatis*.

| Recommended Regimen |
|--|
| Erythromycin (0.5%) ophthalmic ointment in each eye in a single application at birth |

This preparation should be instilled into both eyes of all neonates as soon as possible after delivery, regardless of whether they are delivered vaginally or by cesarean section. Ideally, ointment should be applied using single-use tubes or ampules rather than multiple-use tubes. If prophylaxis is delayed (i.e., not administered in the delivery room), a

monitoring system should be established to ensure that all infants receive prophylaxis.

Erythromycin is the only antibiotic ointment recommended for use in neonates. Silver nitrate and tetracycline ophthalmic ointment is no longer manufactured in the United States, bacitracin is not effective, and povidone iodine has not been studied adequately (582,583). Gentamicin ophthalmic ointment has been associated with severe ocular reactions in neonates and should not be used for ocular prophylaxis (584,585). If erythromycin ointment is not available, infants at risk for exposure to *N. gonorrhoeae* (especially those born to a mother at risk for gonococcal infection or with no prenatal care) can be administered ceftriaxone 25–50 mg/kg IV or IM, not to exceed 125 mg in a single dose (586).

N. gonorrhoeae causes ophthalmia neonatorum relatively infrequently in the United States (587). However, identifying and treating this infection is especially important, because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness (588).

Diagnostic Considerations

Infants at increased risk for gonococcal ophthalmia include those who did not receive ophthalmia prophylaxis and whose mothers had no prenatal care or have a history of STDs or substance abuse. Gonococcal ophthalmia is strongly suspected when intracellular gram-negative diplococci are identified on Gram stain of conjunctival exudate, justifying presumptive treatment for gonorrhea after appropriate cultures and antimicrobial susceptibility testing for *N. gonorrhoeae* are performed. Presumptive treatment for *N. gonorrhoeae* might be indicated for newborns at increased risk for gonococcal ophthalmia who have increased WBCs (but not intracellular gram negative diplococci) in a Gram-stained smear of conjunctival exudate. Nongonococcal causes of neonatal ophthalmia include *Moraxella catarrhalis* and other Neisseria species, organisms that are indistinguishable from *N. gonorrhoeae* on Gram-stained smear but can be differentiated in the microbiology laboratory.

Treatment

Recommended Regimen

Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg

One dose of ceftriaxone is adequate therapy for gonococcal conjunctivitis. Ceftriaxone should be administered cautiously to hyperbilirubinemic infants, especially those born prematurely. No data exist on the use of dual therapy for the treatment of gonococcal ophthalmia. Topical antibiotic therapy

alone is inadequate and unnecessary if systemic treatment is administered.

Other Management Considerations

Appropriate chlamydial testing should be done simultaneously from the inverted eyelid specimen (see Ophthalmia Neonatorum Caused by *C. trachomatis*). Infants who have gonococcal ophthalmia should be evaluated for signs of disseminated infection (e.g., sepsis, arthritis, and meningitis). Infants who have gonococcal ophthalmia should be managed in consultation with an infectious-disease specialist.

Follow-up

Infants who have ophthalmia neonatorum should be managed in consultation with an infectious-disease specialist.

Management of Mothers and Their Sex Partners

Mothers of infants with ophthalmia neonatorum caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partner(s). For more information, see Gonococcal Infections in Adolescents and Adults.

DGI and Gonococcal Scalp Abscesses in Neonates

DGI might present as sepsis, arthritis, or meningitis and is a rare complication of neonatal gonococcal infection. Localized gonococcal infection of the scalp can result from fetal monitoring through scalp electrodes. Detection of gonococcal infection in neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, and joint aspirate. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum are useful for identifying the primary site(s) of infection. Antimicrobial susceptibility testing of all isolates should be performed. Positive Gram-stained smears of exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae*.

Recommended Regimens

Ceftriaxone 25–50 mg/kg/day IV or IM in a single daily dose for 7 days, with a duration of 10–14 days if meningitis is documented

OR

Cefotaxime 25 mg/kg IV or IM every 12 hours for 7 days, with a duration of 10–14 days if meningitis is documented

Ceftriaxone should be administered cautiously to hyperbilirubinemic infants, especially those born prematurely. No data exist on the use of dual therapy for the treatment of DGI or gonococcal scalp abscesses.

Other Management Considerations

Appropriate chlamydial testing should be done simultaneously in neonates with gonococcal infection. For more information, see Chlamydia Infection in Neonates. Infants who have DGI should be managed in consultation with an infectious-disease specialist.

Management of Mothers and Their Sex Partners

Mothers of infants who have DGI or scalp abscesses caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partner(s). For more information, see Gonococcal Infections in Adolescents and Adults.

Neonates Born to Mothers Who Have Gonococcal Infection

Neonates born to mothers who have untreated gonorrhea are at high risk for infection. Neonates should be tested for gonorrhea at exposed sites and treated presumptively for gonorrhea as recommended in these guidelines. No data exist on the use of dual therapy to treat neonates born to mothers who have gonococcal infection.

Recommended Regimen in the Absence of Signs of Gonococcal Infection

Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg

Other Management Considerations

Appropriate chlamydial testing should be done simultaneously in neonates with gonococcal infection. For more information, see Chlamydia Infection in Neonates. Follow-up examination is not required.

Management of Mothers and Their Sex Partners

Mothers who have gonorrhea and their sex partners should be evaluated, tested, and presumptively treated for gonorrhea. For more information, see Gonococcal Infections.

Gonococcal Infections Among Infants and Children

Sexual abuse is the most frequent cause of gonococcal infection in infants and children (see Sexual Assault or Abuse of Children). For preadolescent girls, vaginitis is the most common manifestation of this infection; gonococcal-associated PID after vaginal infection can be less common in preadolescents than adults. Among sexually abused children, anorectal and pharyngeal infections with *N. gonorrhoeae* are frequently asymptomatic.

Diagnostic Considerations

NAAT can be used to test vaginal and urine specimens from girls (see Sexual Assault or Abuse of Children), although data are insufficient to recommend the use of these tests in boys and from extragenital sites (rectum and pharynx) in boys and girls (394). Culture remains the preferred method for diagnosing boys and for detecting infection in specimens obtained from extragenital sites regardless of gender (394). Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. If evidence of disseminated gonococcal infection exists, gonorrhea culture and antimicrobial susceptibility testing should be obtained from relevant clinical sites (see DGI).

Recommended Regimen for Infants and Children Who Weigh ≤ 45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis

Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg IM

Recommended Regimen for Children Who Weigh >45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis

Treat with one of the regimens recommended for adults (see Gonococcal Infections)

Recommended Regimen for Children Who Weigh ≤ 45 kg and Who Have Bacteremia or Arthritis

Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days

Recommended Regimen for Children Who Weigh >45 kg and Who Have Bacteremia or Arthritis

Ceftriaxone 1 g IM or IV in a single dose daily every 24 hours for 7 days

No data exist regarding the use of dual therapy for treating children with gonococcal infection.

Other Management Considerations

Follow-up cultures are unnecessary. Only parenteral cephalosporins (i.e., ceftriaxone) are recommended for use in children. All children found to have gonococcal infections should be tested for *C. trachomatis*, syphilis, and HIV. For a discussion of concerns regarding sexual assault, see Sexual Assault or Abuse of Children.

Diseases Characterized by Vaginal Discharge

Most women will have a vaginal infection, characterized by discharge, itching, or odor, during their lifetime. With the availability of complementary and alternative therapies and over-the-counter medications for candidiasis, many symptomatic women seek these products before or in addition to an evaluation by a medical provider.

Obtaining a medical history alone has been shown to be insufficient for accurate diagnosis of vaginitis and can lead to the inappropriate administration of medication. Therefore, a careful history, examination, and laboratory testing to determine the etiology of vaginal symptoms are warranted. Information on sexual behaviors and practices, gender of sex partners, menses, vaginal hygiene practices (e.g., douching), and self-treatment with medications should be elicited. The three diseases most frequently associated with vaginal discharge are BV (replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *Prevotella* sp., *Mobiluncus* sp., *G. vaginalis*, Ureaplasma, Mycoplasma, and numerous fastidious or uncultivated anaerobes), *T. vaginalis*, and candidiasis. Cervicitis can also cause an abnormal discharge. Although vulvovaginal candidiasis (VVC) is usually not transmitted sexually, it is included in this section because it is frequently diagnosed in women who have vaginal symptoms or are being evaluated for STDs.

Various diagnostic methods are available to identify the etiology of an abnormal vaginal discharge. Clinical laboratory testing can identify the cause of vaginitis in most women and is discussed in detail in the sections of this report dedicated to each condition. In the clinician's office, the cause of vaginal symptoms might be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of fresh samples of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper; an elevated pH (i.e., ≥ 4.5) is common with BV or trichomoniasis. Because pH testing is not highly specific, discharge should be further examined microscopically by first diluting one sample in one or two drops of 0.9% normal saline solution on one slide and a second sample in 10% KOH solution (samples that emit an amine odor immediately upon application of KOH suggest BV or trichomoniasis). Coverslips are then placed on the slides, and they are examined under a microscope at low and high power.

The saline-solution specimen might show motile trichomonads or "clue cells" (i.e., epithelial cells with borders obscured by small bacteria), which are characteristic of BV. The KOH specimen typically is used to identify hyphae or blastospores seen with candidiasis. However, the absence of trichomonads in saline or fungal elements in KOH samples

does not rule out these infections, because the sensitivity of microscopy is approximately 50% compared with NAAT (trichomoniasis) or culture (yeast) (475). The presence of WBCs without evidence of trichomonads or yeast may also suggest cervicitis (see Cervicitis).

In settings where pH paper, KOH, and microscopy are not available, alternative commercially available point-of-care tests or clinical laboratory testing can be used to diagnose vaginitis. The presence of objective signs of vulvar inflammation in the absence of vaginal pathogens after laboratory testing suggests the possibility of mechanical, chemical, allergic, or other noninfectious causes of vulvovaginal signs or symptoms. In patients with persistent symptoms and no clear etiology, referral to a specialist may be helpful.

Bacterial Vaginosis

BV is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp. and *Mobiluncus* sp.), *G. vaginalis*, Ureaplasma, Mycoplasma, and numerous fastidious or uncultivated anaerobes. Some women experience transient vaginal microbial changes, whereas others experience them for longer intervals of time. Among women presenting for care, BV is the most prevalent cause of vaginal discharge or malodor; however, in a nationally representative survey, most women with BV were asymptomatic (203).

BV is associated with having multiple male or female partners, a new sex partner, douching, lack of condom use, and lack of vaginal lactobacilli; women who have never been sexually active are rarely affected (589). The cause of the microbial alteration that precipitates BV is not fully understood, and whether BV results from acquisition of a single sexually transmitted pathogen is not known. Nonetheless, women with BV are at increased risk for the acquisition of some STDs (e.g., HIV, *N. gonorrhoeae*, *C. trachomatis*, and HSV-2), complications after gynecologic surgery, complications of pregnancy, and recurrence of BV (590–593). BV also increases the risk for HIV transmission to male sex partners (594). Although BV-associated bacteria can be found in the male genitalia, treatment of male sex partners has not been beneficial in preventing the recurrence of BV (595).

Diagnostic Considerations

BV can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) (596) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli (i.e., long Gram-positive rods), Gram-negative

and Gram-variable rods and cocci (i.e., *G. vaginalis*, *Prevotella*, *Porphyromonas*, and peptostreptococci), and curved Gram-negative rods (i.e., *Mobiluncus*) characteristic of BV. Clinical criteria require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- clue cells (e.g., vaginal epithelial cells studded with adherent coccobacilli) on microscopic examination;
- pH of vaginal fluid >4.5; or
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

Detection of three of these criteria has been correlated with results by Gram stain (597). Other tests, including Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test for high concentrations of *G. vaginalis*, and the OSOM BV Blue test (Sekisui Diagnostics, Framingham, MA), which detects vaginal fluid sialidase activity, have acceptable performance characteristics compared with Gram stain. Although a prolineaminopeptidase card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is still underway. Detection of specific organisms might be predictive of BV by PCR (598,599). Additional validation is needed before these tests can be recommended to diagnose BV. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity and specificity.

Treatment

Treatment is recommended for women with symptoms. The established benefits of therapy in nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits to treatment include reduction in the risk for acquiring *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, HIV, and herpes simplex type 2 (592,593,600).

| Recommended Regimens |
|--|
| Metronidazole 500 mg orally twice a day for 7 days OR |
| Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days OR |
| Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days |

Alcohol consumption should be avoided during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for

24 hours after completion of metronidazole. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

Women should be advised to refrain from sexual activity or use condoms consistently and correctly during the treatment regimen. Douching might increase the risk for relapse, and no data support the use of douching for treatment or relief of symptoms.

| Alternative Regimens |
|---|
| Tinidazole 2 g orally once daily for 2 days OR |
| Tinidazole 1 g orally once daily for 5 days OR |
| Clindamycin 300 mg orally twice daily for 7 days OR |
| Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days* |
| * Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and vaginal contraceptive diaphragms). Use of such products within 72 hours following treatment with clindamycin ovules is not recommended. |

Alcohol consumption should be avoided during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for 72 hours after completion of tinidazole.

Alternative regimens include several tinidazole regimens (601) or clindamycin (oral or intravaginal) (602). An additional regimen includes metronidazole (750-mg extended release tablets orally once daily for 7 days); however, data on the performance of this alternative regimen are limited.

Certain studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV and restore normal flora (603–607). Overall, no studies support the addition of any available lactobacillus formulations or probiotic as an adjunctive or replacement therapy in women with BV. Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

Other Management Considerations

All women with BV should be tested for HIV and other STDs.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrent BV is common, women should be advised to return for evaluation if symptoms recur. Detection of certain BV-associated organisms has been associated with antimicrobial resistance and might be predictive of risk for subsequent treatment failure (608–613). Limited data are available regarding optimal management strategies for

women with persistent or recurrent BV. Using a different recommended treatment regimen can be considered in women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence (614). For women with multiple recurrences after completion of a recommended regimen, 0.75% metronidazole gel twice weekly for 4–6 months has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued (615). Limited data suggest that an oral nitroimidazole (metronidazole or tinidazole 500 mg twice daily for 7 days) followed by intravaginal boric acid 600 mg daily for 21 days and then suppressive 0.75% metronidazole gel twice weekly for 4–6 months for those women in remission might be an option for women with recurrent BV (616). Monthly oral metronidazole 2 g administered with fluconazole 150 mg has also been evaluated as suppressive therapy; this regimen reduced the incidence of BV and promoted colonization with normal vaginal flora (617).

Management of Sex Partners

Data from clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s) (595). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

Allergy, Intolerance, or Adverse Reactions

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole or tinidazole. Intravaginal metronidazole gel can be considered for women who are not allergic to metronidazole but do not tolerate oral metronidazole. It is advised to avoid consuming alcohol during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

Pregnancy

Treatment is recommended for all symptomatic pregnant women. Studies have been undertaken to determine the efficacy of BV treatment among this population, including two trials demonstrating that metronidazole was efficacious during pregnancy using the 250-mg regimen (618,619); however, metronidazole administered at 500 mg twice daily can be used. One trial involving a limited number of participants revealed treatment with oral metronidazole 500 mg twice daily to be equally effective as metronidazole gel, with cure rates of 70% using Amsel criteria to define cure (620). Another trial demonstrated a cure rate of 85% using Gram-stain criteria

after treatment with oral clindamycin (621). Multiple studies and meta-analyses have failed to demonstrate an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns (622,623). Although older studies indicated a possible link between use of vaginal clindamycin during pregnancy and adverse outcomes for the newborn, newer data demonstrate that this treatment approach is safe for pregnant women (624). Because oral therapy has not been shown to be superior to topical therapy for treating symptomatic BV in effecting cure or preventing adverse outcomes of pregnancy, symptomatic pregnant women can be treated with either of the oral or vaginal regimens recommended for nonpregnant women. Although adverse pregnancy outcomes, including premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infection, and postpartum endometritis have been associated with symptomatic BV in some observational studies, treatment of BV in pregnant women can reduce the signs and symptoms of vaginal infection. A meta-analysis has concluded that no antibiotic regimen prevented preterm birth (early or late) in women with BV (symptomatic or asymptomatic). However, in one study, oral BV therapy reduced the risk for late miscarriage, and in two additional studies, such therapy decreased adverse outcomes in the neonate (625).

Treatment of asymptomatic BV among pregnant women who are at high risk for preterm delivery (i.e., those with a previous preterm birth) has been evaluated by several studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery: one showed harm (626), two showed no benefit (627,628), and four demonstrated benefit (618,619,629,630).

Similarly, data are inconsistent regarding whether treatment of asymptomatic BV among pregnant women who are at low risk for preterm delivery reduces adverse outcomes of pregnancy. One trial demonstrated a 40% reduction in spontaneous preterm birth among women using oral clindamycin during weeks 13–22 of gestation (630). Several additional trials have shown that intravaginal clindamycin given at an average gestation of >20 weeks did not reduce likelihood of preterm birth (628,631–633). Therefore, evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth (111).

Although metronidazole crosses the placenta, no evidence of teratogenicity or mutagenic effects in infants has been found in multiple cross-sectional and cohort studies of pregnant women (634). Data suggest that metronidazole therapy poses low risk in pregnancy (317).

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections in infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but remain less than maternal plasma levels (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>). Although several reported case series found no evidence of metronidazole-associated adverse effects in breastfed infants, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a single 2 g dose of metronidazole (635). Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding (636,637). Data from studies of human subjects are limited regarding the use of tinidazole in pregnancy; however, animal data suggest that such therapy poses moderate risk. Thus tinidazole should be avoided during pregnancy (317).

HIV Infection

BV appears to recur with higher frequency in women who have HIV infection (638). Women with HIV who have BV should receive the same treatment regimen as those who do not have HIV infection.

Trichomoniasis

Trichomoniasis is the most prevalent nonviral sexually transmitted infection in the United States, affecting an estimated 3.7 million persons (533). Health disparities persist in the epidemiology of *T. vaginalis* infection in the United States: 13% of black women are affected compared with 1.8% of non-Hispanic white women (639). *T. vaginalis* infection affects >11% of women aged ≥40 years (640), and particularly high prevalence has been detected among STD clinic patients (641) (26% of symptomatic women and 6.5% asymptomatic women tested) and incarcerated persons (9%–32% of incarcerated women [135,136,640,642,643] and 2%–9% of incarcerated men) (136,137,644,645). The prevalence of trichomoniasis in MSM is low (646,647).

Some infected men have symptoms of urethritis, epididymitis, or prostatitis, and some infected women have vaginal discharge that might be diffuse, malodorous, or yellow-green with or without vulvar irritation. However, most infected persons (70%–85%) have minimal or no symptoms, and untreated infections might last for months to years (86,639,648,649). Although partners might be unaware of their infection, it is readily passed between sex partners during penile-vaginal sex (650). Among persons who are sexually active, the best way to prevent trichomoniasis is through consistent and correct use of condoms during all penile-vaginal sexual encounters

(22). Partners of men who have been circumcised might have a somewhat reduced risk of *T. vaginalis* infection (56,651). Douching is not recommended because it might increase the risk for vaginal infections, including trichomoniasis (652).

T. vaginalis infection is associated with two- to threefold increased risk for HIV acquisition (653–656), preterm birth, and other adverse pregnancy outcomes among pregnant women. Among women with HIV infection, *T. vaginalis* infection is associated with increased risk for PID (657–659). Routine screening of asymptomatic women with HIV infection for *T. vaginalis* is recommended because of the adverse events associated with asymptomatic trichomoniasis and HIV infection.

Diagnostic testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge. Screening might be considered for persons receiving care in high-prevalence settings (e.g., STD clinics and correctional facilities) and for asymptomatic persons at high risk for infection (e.g., persons with multiple sex partners, exchanging sex for payment, illicit drug use, or a history of STD). However, data are lacking on whether screening and treatment for asymptomatic trichomoniasis in high prevalence settings or persons at high risk can reduce any adverse health events and health disparities or reduce community burden of infection. Decisions about screening might be informed by local epidemiology of *T. vaginalis* infection.

Whether the rectum can be a reservoir for *T. vaginalis* infection is unclear; data are needed to clarify whether this occasional finding might reflect recent depositing contamination in up to 5% of persons reporting recent receptive anal sex (660,661). Further, the efficacy, benefit, and cost-effectiveness of rectal screening are unknown; therefore, rectal testing for *T. vaginalis* is not recommended. Similarly, oral testing for *T. vaginalis* is not recommended because of a lack of evidence for oral infections. *T. vaginalis* infection is not a nationally notifiable condition in the United States (118,662).

Diagnostic Considerations

The use of highly sensitive and specific tests is recommended for detecting *T. vaginalis*. Among women, NAAT is highly sensitive, often detecting three to five times more *T. vaginalis* infections than wet-mount microscopy, a method with poor sensitivity (51%–65%) (663,664). The APTIMA *T. vaginalis* assay (Hologic Gen-Probe, San Diego, CA) is FDA-cleared for detection of *T. vaginalis* from vaginal, endocervical, or urine specimens from women. This assay detects RNA by transcription-mediated amplification with a clinical sensitivity of 95.3%–100% and specificity of 95.2%–100% (665,666). Among women, vaginal swab and urine have up to 100% concordance (663). As analyte-specific reagents, this assay can

be used with urine or urethral swabs from men if validated per CLIA regulations. The sale, distribution, and use of analyte-specific reagents are allowed under 21 C.F.R. 809.30 pertaining to in vitro diagnostic products for human use. For *T. vaginalis* diagnosis in men, the sensitivity of self-collected penile-meatal swabs was higher than that of urine in one study (80% and 39%, respectively) (667). The BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, New Jersey) is FDA-cleared for detection of *T. vaginalis* from endocervical, vaginal, or urine specimens from women. Although it might be feasible to perform these tests on the same specimen used for chlamydia and gonorrhea screening, the epidemiology of trichomoniasis is distinct and should not be overlooked in older adults.

Other FDA-cleared tests to detect *T. vaginalis* in vaginal secretions include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, MA), an antigen-detection test using immunochromatographic capillary flow dipstick technology that can be performed at the point of care, and the Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *Candida albicans*. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, with sensitivity 82%–95% and specificity 97%–100% (666,668). Self-testing might become an option, as a study of 209 young women aged 14–22 years found that >99% could correctly perform and interpret her own self-test using the OSOM assay, with a high correlation with clinician interpretation (96% agreement, $\kappa = 0.87$) (669). The results of the Affirm VP III are available within 45 minutes. Sensitivity and specificity are 63% and 99.9%, respectively, compared with culture and TMA; sensitivity might be higher among women who are symptomatic (670,671). Neither the OSOM nor the Affirm VP III test is FDA-cleared for use with specimens obtained from men.

Culture was considered the gold standard method for diagnosing *T. vaginalis* infection before molecular detection methods became available. Culture has a sensitivity of 75%–96% and a specificity of up to 100% (475). In women, vaginal secretions are the preferred specimen type for culture, as urine culture is less sensitive (475,672,673). In men, culture specimens require a urethral swab, urine sediment, and/or semen. To improve yield, multiple specimens from men can be used to inoculate a single culture.

The most common method for *T. vaginalis* diagnosis might be microscopic evaluation of wet preparations of genital secretions because of convenience and relatively low cost. Unfortunately, the sensitivity of wet mount is low (51%–65%) in vaginal specimens (475,666) and lower in specimens from men (e.g., urethral specimens, urine sediment, and semen).

Clinicians using wet mounts should attempt to evaluate slides immediately because sensitivity declines as evaluation is delayed, decreasing by up to 20% within 1 hour after collection (674,675). When highly sensitive (e.g., NAAT) testing on specimens is not feasible, a testing algorithm (e.g., wet mount first, followed by NAAT if negative) can improve diagnostic sensitivity in persons with an initial negative result by wet mount (475). Although *T. vaginalis* may be an incidental finding on a Pap test, neither conventional nor liquid-based Pap tests are considered diagnostic tests for trichomoniasis, because false negatives and false positives can occur.

Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection and might reduce transmission. Likelihood of adverse outcomes in women with HIV also is reduced with *T. vaginalis* therapy.

Recommended Regimen

Metronidazole 2 g orally in a single dose
OR
Tinidazole 2 g orally in a single dose

Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days

Alcohol consumption should be avoided during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

The nitroimidazoles are the only class of antimicrobial medications known to be effective against *T. vaginalis* infections. Of these drugs, metronidazole and tinidazole have been cleared by FDA for the oral or parenteral treatment of trichomoniasis. Tinidazole is generally more expensive, reaches higher levels in serum and the genitourinary tract, has a longer half-life than metronidazole (12.5 hours versus 7.3 hours), and has fewer gastrointestinal side effects (676–678). In randomized clinical trials, recommended metronidazole regimens have resulted in cure rates of approximately 84%–98% (679–681), and the recommended tinidazole regimen has resulted in cure rates of approximately 92%–100% (680,682–685). Randomized controlled trials comparing single 2 g doses of metronidazole and tinidazole suggest that tinidazole is equivalent or superior to metronidazole in achieving parasitologic cure and resolution of symptoms (686).

Metronidazole gel does not reach therapeutic levels in the urethra and perivaginal glands. Because it is less efficacious than oral metronidazole, it is not recommended.

Other Management Considerations

Providers should advise persons infected with *T. vaginalis* to abstain from sex until they and their sex partners are treated (i.e., when therapy has been completed and any symptoms have resolved). Testing for other STDs including HIV should be performed in persons infected with *T. vaginalis*.

Follow-up

Because of the high rate of reinfection among women treated for trichomoniasis (17% within 3 months in one study) (86), retesting for *T. vaginalis* is recommended for all sexually active women within 3 months following initial treatment regardless of whether they believe their sex partners were treated (see Diagnostic Considerations). Testing by nucleic acid amplification can be conducted as soon as 2 weeks after treatment (687,688). Data are insufficient to support retesting men.

Management of Sex Partners

Concurrent treatment of all sex partners is critical for symptomatic relief, microbiologic cure, and prevention of transmission and reinfections. Current partners should be referred for presumptive therapy to avoid reinfection. Partners should be advised to abstain from intercourse until they and their sex partners have been adequately treated and any symptoms have resolved. EPT might have a role in partner management for trichomoniasis (97,98,689) and can be used in states where permissible by law; however, no one partner management intervention has been shown to be superior in reducing reinfection rates. Though no definitive data exist to guide treatment for partners of persons with persistent or recurrent trichomoniasis in whom nonadherence and reinfection are unlikely, partners benefit from undergoing evaluation and receiving the same regimen as the patient (see Persistent or Recurrent Trichomoniasis).

Persistent or Recurrent Trichomoniasis

Persistent or recurrent infection caused by antimicrobial-resistant *T. vaginalis* or other causes should be distinguished from the possibility of reinfection from an untreated sex partner. Although most recurrent *T. vaginalis* infections are thought to result from reinfection, some infections might be attributed to antimicrobial resistance. Metronidazole resistance occurs in 4%–10% of cases of vaginal trichomoniasis (690,691), and tinidazole resistance in 1% (691). In general, *T. vaginalis* isolates have lower minimum lethal concentrations to

tinidazole than metronidazole (692). Emerging nitroimidazole-resistant trichomoniasis is concerning, because few alternatives to standard therapy exist. Single-dose therapy should be avoided for treating recurrent trichomoniasis that is not likely a result of reinfection. If treatment failure has occurred with metronidazole 2 g single dose and reinfection is excluded, the patient (and their partner[s]) can be treated with metronidazole 500 mg orally twice daily for 7 days. If this regimen fails, clinicians should consider treatment with metronidazole or tinidazole at 2 g orally for 7 days. If several 1-week regimens have failed in a person who is unlikely to have nonadherence or reinfection, testing of the organism for metronidazole and tinidazole susceptibility is recommended (693). CDC has experience with susceptibility testing for nitroimidazole-resistant *T. vaginalis* and treatment management of infected persons and can provide assistance (telephone: 404-718-4141; website: <http://www.cdc.gov/std>). Higher dose tinidazole at 2–3 g for 14 days, often in combination with intravaginal tinidazole, can be considered in cases of nitroimidazole-resistant infections; however, such cases should be managed in consultation with an expert.

Alternative regimens might be effective but have not been systematically evaluated; therefore, consultation with an infectious-disease specialist is recommended. The most anecdotal experience has been with intravaginal paromomycin in combination with high-dose tinidazole (694–696); clinical improvement has been reported with other alternative regimens including intravaginal boric acid (697,698) and nitazoxanide (699). The following topically applied agents have shown minimal success (<50%) and are not recommended: intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate (700). No other topical microbicide has been shown to be effective against trichomoniasis (701).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an IgE mediated-type allergy to a nitroimidazole can be managed by metronidazole desensitization according to a published regimen (702) and in consultation with a specialist.

Pregnancy

T. vaginalis infection in pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of a low birthweight infant (658,703–705). Although metronidazole treatment produces parasitologic cure, certain trials have shown no significant difference in perinatal morbidity following

metronidazole treatment. One trial suggested the possibility of increased preterm delivery in women with *T. vaginalis* infection who received metronidazole treatment (706), yet study limitations prevented definitive conclusions regarding the risks of treatment. More recent, larger studies have shown no positive or negative association between metronidazole use during pregnancy and adverse outcomes of pregnancy (634,707–710). If treatment is considered, the recommended regimen in pregnant women is metronidazole 2 g orally in a single dose. Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment. Treatment of *T. vaginalis* infection can relieve symptoms of vaginal discharge in pregnant women and reduce sexual transmission to partners. Although perinatal transmission of trichomoniasis is uncommon, treatment also might prevent respiratory or genital infection of the newborn (711,712). Clinicians should counsel symptomatic pregnant women with trichomoniasis regarding the potential risks for and benefits of treatment and about the importance of partner treatment and condom use in the prevention of sexual transmission.

The benefit of routine screening for *T. vaginalis* in asymptomatic pregnant women has not been established. However, screening at the first prenatal visit and prompt treatment, as appropriate, are recommended for pregnant women with HIV infection, because *T. vaginalis* infection is a risk factor for vertical transmission of HIV (713). Pregnant women with HIV who are treated for *T. vaginalis* infection should be retested 3 months after treatment.

Although metronidazole crosses the placenta, data suggest that it poses a low risk to pregnant women (317). No evidence of teratogenicity or mutagenic effects in infants has been found in multiple cross-sectional and cohort studies of pregnant women (708–710,714). Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are lower than those used to treat infections in infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but remain less than maternal plasma levels (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>). Although several reported case series found no evidence of adverse effects in infants exposed to metronidazole in breast milk, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a single 2 g dose of metronidazole (635). Maternal treatment with metronidazole (400 mg three times daily for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods of time (636,637).

Data from studies involving human subjects are limited regarding use of tinidazole in pregnancy; however, animal data suggest this drug poses moderate risk. Thus, tinidazole should be avoided in pregnant women, and breastfeeding should be deferred for 72 hours following a single 2-g dose of tinidazole (<http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>).

HIV Infection

Up to 53% of women with HIV infection also are infected with *T. vaginalis* (715,716). *T. vaginalis* infection in these women is significantly associated with PID (659), and treatment of trichomoniasis is associated with significant decreases in genital-tract HIV viral load and viral shedding (717,718). For these reasons, routine screening and prompt treatment are recommended for all women with HIV infection; screening should occur at entry to care and then at least annually thereafter. A randomized clinical trial involving women with HIV infection and *T. vaginalis* infection demonstrated that a single dose of metronidazole 2 g orally was less effective than 500 mg twice daily for 7 days (719). Thus, to improve cure rates, women with HIV infection who receive a diagnosis of *T. vaginalis* infection should be treated with metronidazole 500 mg orally twice daily for 7 days (rather than with a 2-g single dose of metronidazole). Factors that might interfere with standard single-dose treatment for trichomoniasis in these women include high rates of asymptomatic BV co-infections, use of antiretroviral therapy, changes in vaginal ecology, and impaired immunity (656,720,721).

Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection and might reduce transmission. Likelihood of adverse outcomes in women with HIV is also reduced with *T. vaginalis* therapy.

Recommended Regimen for Women with HIV Infection

Metronidazole 500 mg orally twice daily for 7 days

In women with HIV infection who receive a diagnosis of *T. vaginalis* infection, retesting is recommended within 3 months following initial treatment; NAAT is encouraged because of higher sensitivity of these tests. Data are insufficient to recommend routine screening, alternative treatment regimens of longer duration, or retesting in men.

Vulvovaginal Candidiasis

VVC usually is caused by *C. albicans* but can occasionally be caused by other *Candida* sp. or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia,

external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated (Box 3). Approximately 10%–20% of women will have complicated VVC, requiring special diagnostic and therapeutic considerations.

Uncomplicated VVC

Diagnostic Considerations

A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, and thick curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates budding yeasts, hyphae, or pseudohyphae or 2) a culture or other test yields a positive result for a yeast species. *Candida* vaginitis is associated with a normal vaginal pH (<4.5). Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with

BOX 3. Classification of vulvovaginal candidiasis

| |
|--|
| <p>Uncomplicated VVC</p> <ul style="list-style-type: none"> • Sporadic or infrequent VVC <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • Mild-to-moderate VVC <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • Likely to be <i>Candida albicans</i> <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • Nonimmunocompromised women <p>Complicated VVC</p> <ul style="list-style-type: none"> • Recurrent VVC <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Severe VVC <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Nonalbicans candidiasis <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Women with diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids) <p>Abbreviation: HIV = human immunodeficiency virus; VVC = vulvovaginal candidiasis.</p> |
|--|

KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should be treated. For those with negative wet mounts but existing signs or symptoms, vaginal cultures for *Candida* should be considered. If *Candida* cultures cannot be performed for these women, empiric treatment can be considered. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment, because approximately 10%–20% of women harbor *Candida* sp. and other yeasts in the vagina. PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis. VVC can occur concomitantly with STDs. Most healthy women with uncomplicated VVC have no identifiable precipitating factors.

Treatment

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy.

| Recommended Regimens |
|---|
| <p>Over-the-Counter Intravaginal Agents:</p> <p>Clotrimazole 1% cream 5 g intravaginally daily for 7–14 days OR</p> <p>Clotrimazole 2% cream 5 g intravaginally daily for 3 days OR</p> <p>Miconazole 2% cream 5 g intravaginally daily for 7 days OR</p> <p>Miconazole 4% cream 5 g intravaginally daily for 3 days OR</p> <p>Miconazole 100 mg vaginal suppository, one suppository daily for 7 days OR</p> <p>Miconazole 200 mg vaginal suppository, one suppository for 3 days OR</p> <p>Miconazole 1,200 mg vaginal suppository, one suppository for 1 day OR</p> <p>Tioconazole 6.5% ointment 5 g intravaginally in a single application</p> <p>Prescription Intravaginal Agents:</p> <p>Butoconazole 2% cream (single dose bioadhesive product), 5 g intravaginally in a single application OR</p> <p>Terconazole 0.4% cream 5 g intravaginally daily for 7 days OR</p> <p>Terconazole 0.8% cream 5 g intravaginally daily for 3 days OR</p> <p>Terconazole 80 mg vaginal suppository, one suppository daily for 3 days</p> <p>Oral Agent:</p> <p>Fluconazole 150 mg orally in a single dose</p> |

The creams and suppositories in these regimens are oil-based and might weaken latex condoms and diaphragms. Refer to condom product labeling for further information. Intravaginal preparations of clotrimazole, miconazole, and tioconazole are

available over-the-counter (OTC). Even women who have previously received a diagnosis of VVC by a clinician are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose symptoms persist after using an OTC preparation or who has a recurrence of symptoms within 2 months after treatment for VVC should be clinically evaluated and tested. Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies, which can in turn result in adverse outcomes.

Follow-Up

Follow-up typically is not required. However, women in whom symptoms persist or recur after treatment of initial symptoms should be instructed to return for follow-up visits.

Management of Sex Partners

Uncomplicated VVC is not usually acquired through sexual intercourse; thus, data do not support treatment of sex partners. A minority of male sex partners have balanitis, characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Topical agents usually cause no systemic side effects, although local burning or irritation might occur. Oral azoles occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Clinically important interactions can occur when oral azoles agents are administered with other drugs (722).

Complicated VVC

Diagnostic Considerations

Vaginal cultures should be obtained from women with complicated VVC to confirm clinical diagnosis and identify unusual species, including nonalbicans species. *C. glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy. Although *C. albicans* azole resistance is possibly becoming more common in vaginal isolates (723,724), susceptibility testing is usually not warranted for individual treatment guidance.

Recurrent Vulvovaginal Candidiasis

Recurrent Vulvovaginal Candidiasis (RVVC), usually defined as four or more episodes of symptomatic VVC within 1 year, affects a small percentage of women (<5%). The pathogenesis

of RVVC is poorly understood, and most women with RVVC have no apparent predisposing or underlying conditions. *C. glabrata* and other nonalbicans *Candida* species are observed in 10%–20% of women with RVVC. Conventional antimycotic therapies are not as effective against these nonalbicans species as against *C. albicans*.

Treatment

Each individual episode of RVVC caused by *C. albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [day 1, 4, and 7]) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line maintenance regimen. If this regimen is not feasible, topical treatments used intermittently can also be considered. Suppressive maintenance therapies are effective in reducing RVVC. However, 30%–50% of women will have recurrent disease after maintenance therapy is discontinued. Symptomatic women who remain culture-positive despite maintenance therapy should be managed in consultation with a specialist.

Severe VVC

Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential oral doses (second dose 72 hours after initial dose) is recommended.

Nonalbicans VVC

Because at least 50% of women with positive cultures for nonalbicans *Candida* might be minimally symptomatic or have no symptoms and because successful treatment is often difficult, clinicians should make every effort to exclude other causes of vaginal symptoms in women with nonalbicans yeast (725). The optimal treatment of nonalbicans VVC remains unknown. Options include longer duration of therapy (7–14 days) with a nonfluconazole azole regimen (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70% (726). If symptoms recur, referral to a specialist is advised.

Management of Sex Partners

No data exist to support the treatment of sex partners of patients with complicated VVC. Therefore, no recommendation can be made.

Special Considerations

Compromised Host

Women with underlying immunodeficiency, those with poorly controlled diabetes or other immunocompromising conditions (e.g., HIV), and those receiving immunosuppression therapy (e.g., corticosteroid treatment) do not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7–14 days) conventional treatment is necessary.

Pregnancy

VVC occurs frequently during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women.

HIV Infection

Vaginal *Candida* colonization rates among women with HIV infection are higher than among seronegative women with similar demographic and risk behavior characteristics, and the colonization rates correlate with increasing severity of immunosuppression. Symptomatic VVC is also more frequent in women with HIV infection and similarly correlates with severity of immunodeficiency. In addition, among women with HIV infection, systemic azole exposure is associated with the isolation of nonalbicans *Candida* species from the vagina.

On the basis of available data, therapy for uncomplicated and complicated VVC in women with HIV infection should not differ from that for seronegative women. Although long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC (727), this regimen is not recommended for women with HIV infection in the absence of complicated VVC (247). Although VVC is associated with increased HIV seroconversion in HIV-negative women and increased HIV cervicovaginal levels in women with HIV infection, the effect of treatment for VVC on HIV acquisition and transmission remains unknown.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis (728). Sexually

transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases. Recent studies suggest that the proportion of PID cases attributable to *N. gonorrhoeae* or *C. trachomatis* is declining; of women who received a diagnosis of acute PID, <50% test positive for either of these organisms (270,729,730). Microorganisms that comprise the vaginal flora (e.g., anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) have been associated with PID (731). In addition, cytomegalovirus (CMV), *M. hominis*, *U. urealyticum*, and *M. genitalium* might be associated with some PID cases (264,265,267,732). Newer data suggest that *M. genitalium* might play a role in the pathogenesis of PID (270,487) and might be associated with milder symptoms (267), although one study failed to demonstrate a significant increase in PID following detection of *M. genitalium* in the lower genital tract (733). All women who receive a diagnosis of acute PID should be tested for HIV, as well as gonorrhea and chlamydia, using NAAT. The value of testing women with PID for *M. genitalium* is unknown, and there is no commercially available diagnostic test that has been cleared by FDA for use in the United States (see *Mycoplasma genitalium*).

Screening and treating sexually active women for chlamydia reduces their risk for PID (456,682). Although BV is associated with PID, whether the incidence of PID can be reduced by identifying and treating women with BV is unclear (731,734).

Diagnostic Considerations

Acute PID is difficult to diagnose because of the wide variation in symptoms and signs associated with this condition. Many women with PID have subtle or nonspecific symptoms or are asymptomatic. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper reproductive tract. Laparoscopy can be used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, this diagnostic tool frequently is not readily available, and its use is not easily justifiable when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and might not detect subtle inflammation of the fallopian tubes. Consequently, a diagnosis of PID usually is based on imprecise clinical findings (735,736).

Data indicate that a clinical diagnosis of symptomatic PID has a PPV for salpingitis of 65%–90% compared with laparoscopy (737–739). The PPV of a clinical diagnosis of acute PID depends on the epidemiologic characteristics of the population, with higher PPVs among sexually active young women (particularly adolescents), women attending STD clinics, and those who live in communities with high rates of gonorrhea or chlamydia. Regardless of PPV, no single

historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Combinations of diagnostic findings that improve either sensitivity (i.e., detect more women who have PID) or specificity (i.e., exclude more women who do not have PID) do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID and reduces the number of women with PID who are identified.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are not diagnosed 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, and vaginal discharge). Even women with mild or asymptomatic PID might be at risk for infertility (740). Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women, health-care providers should maintain a low threshold for the diagnosis of PID (729). The following recommendations for diagnosing PID are intended to help health-care providers recognize when PID should be suspected and when additional information should be obtained to increase diagnostic certainty. Diagnosis and management of other common causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, ovarian cyst, and functional pain) are unlikely to be impaired by initiating antimicrobial therapy for PID.

Presumptive treatment for PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if one or more of the following minimum clinical criteria are present on pelvic examination:

- cervical motion tenderness
or
- uterine tenderness
or
- adnexal tenderness.

The requirement that all three minimum criteria be present before the initiation of empiric treatment could result in insufficient sensitivity for the diagnosis of PID. After deciding whether to initiate empiric treatment, clinicians should also consider the risk profile for STDs.

More elaborate diagnostic evaluation frequently is needed because incorrect diagnosis and management of PID might cause unnecessary morbidity. For example, the presence of signs of lower-genital-tract inflammation (predominance of leukocytes in vaginal secretions, cervical exudates, or cervical friability), in addition to one of the three minimum criteria, increases the specificity of the diagnosis. One or more of the following additional criteria can be used to enhance the

specificity of the minimum clinical criteria and support a diagnosis of PID:

- oral temperature $>101^{\circ}\text{F}$ ($>38.3^{\circ}\text{C}$);
- abnormal cervical mucopurulent discharge or cervical friability;
- presence of abundant numbers of WBC on saline microscopy of vaginal fluid;
- elevated erythrocyte sedimentation rate;
- elevated C-reactive protein; and
- laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*.

Most women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (i.e., wet prep). If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be considered. A wet prep of vaginal fluid also can detect the presence of concomitant infections (e.g., BV and trichomoniasis).

The most specific criteria for diagnosing PID include:

- endometrial biopsy with histopathologic evidence of endometritis;
- transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); or
- laparoscopic findings consistent with PID.

A diagnostic evaluation that includes some of these more extensive procedures might be warranted in some cases. Endometrial biopsy is warranted in women undergoing laparoscopy who do not have visual evidence of salpingitis, because endometritis is the only sign of PID for some women.

Treatment

PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens. Several parenteral and oral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up (741,742). However, only a limited number of investigations have assessed and compared these regimens with regard to elimination of infection in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens (730,735,743). The optimal treatment regimen and long-term outcome of early treatment of women with subclinical PID are unknown. All regimens used to treat PID should also be effective against *N. gonorrhoeae* and *C. trachomatis* because

negative endocervical screening for these organisms does not rule out upper-reproductive-tract infection. The need to eradicate anaerobes from women who have PID has not been determined definitively. Anaerobic bacteria have been isolated from the upper-reproductive tract of women who have PID, and data from in vitro studies have revealed that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. BV is present in many women who have PID (731,734). Until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made, because prevention of long-term sequelae is dependent on early administration of appropriate antibiotics. When selecting a treatment regimen, health-care providers should consider availability, cost, and patient acceptance (742). In women with PID of mild or moderate clinical severity, parenteral and oral regimens appear to have similar efficacy. The decision of whether hospitalization is necessary should be based on provider judgment and whether the woman meets any of the following suggested criteria:

- surgical emergencies (e.g., appendicitis) cannot be excluded;
- tubo-ovarian abscess;
- pregnancy;
- severe illness, nausea and vomiting, or high fever;
- unable to follow or tolerate an outpatient oral regimen;
- or
- no clinical response to oral antimicrobial therapy.

No evidence is available to suggest that adolescents have improved outcomes from hospitalization for treatment of PID, and the clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women.

Parenteral Treatment

Several randomized trials have demonstrated the efficacy of parenteral regimens (734,741,742). Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement. In women with tubo-ovarian abscesses, at least 24 hours of inpatient observation is recommended.

Recommended Parenteral Regimens

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

Because of the pain associated with intravenous infusion, doxycycline should be administered orally when possible. Oral and IV administration of doxycycline provide similar bioavailability. Although use of a single daily dose of gentamicin has not been evaluated for the treatment of PID, it is efficacious in analogous situations.

When using the parenteral cefotetan or cefoxitin regimens, oral therapy with doxycycline 100 mg twice daily can be used 24–48 hours after clinical improvement to complete the 14 days of therapy for the clindamycin/gentamicin regimen, and oral therapy with clindamycin (450 mg orally four times daily) or doxycycline (100 mg twice daily) can be used to complete the 14 days of therapy. However, when tubo-ovarian abscess is present, clindamycin (450 mg orally four times daily) or metronidazole (500 mg twice daily) should be used to complete at least 14 days of therapy with doxycycline to provide more effective anaerobic coverage than doxycycline alone.

Limited data are available to support use of other parenteral second- or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone). In addition, these cephalosporins are less active than cefotetan or cefoxitin against anaerobic bacteria.

Alternative Parenteral Regimens

Ampicillin/sulbactam plus doxycycline has been investigated in at least one clinical trial and has broad-spectrum coverage (744). Ampicillin/sulbactam plus doxycycline is effective against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. Another trial demonstrated high short-term clinical cure rates with azithromycin, either as monotherapy for 1 week (500 mg IV daily for 1 or 2 doses followed by 250 mg orally for 5–6 days) or combined with a 12-day course of metronidazole (745). Limited data are available to support the use of other parenteral regimens.

Alternative Parenteral Regimen

Ampicillin/Sulbactam 3 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours

Intramuscular/Oral Treatment

Intramuscular/oral therapy can be considered for women with mild-to-moderately severe acute PID, because the clinical outcomes among women treated with these regimens are similar to those treated with intravenous therapy (729). Women who do not respond to IM/oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered intravenous therapy.

Recommended Intramuscular/Oral Regimens

Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH* or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and **Probenecid**, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation **cephalosporin** (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH* or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

* 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 regimens with third-generation cephalosporins should be considered (Source: Walker CK, Wiesenfeld HC. Antibiotic therapy for acute pelvic inflammatory disease: the 2006 CDC Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 2007;28[Supp 1]:S29–36).

These regimens provide coverage against frequent etiologic agents of PID, but the optimal choice of a cephalosporin is unclear. Cefoxitin, a second-generation cephalosporin, has better anaerobic coverage than ceftriaxone, and in combination with probenecid and doxycycline has been effective in short-term clinical response in women with PID. Ceftriaxone has better coverage against *N. gonorrhoeae*. The addition of metronidazole will also effectively treat BV, which is frequently associated with PID.

Alternative IM/Oral Regimens

Although information regarding other IM and oral regimens is limited, a few have undergone at least one clinical trial and have demonstrated broad-spectrum coverage. Azithromycin has demonstrated short-term clinical effectiveness in one randomized trial when used as monotherapy (500 mg IV daily for 1–2 doses, followed by 250 mg orally daily for 12–14 days) or in combination with metronidazole (745), and in another study, it was effective when used 1 g orally once a week for

2 weeks in combination with ceftriaxone 250 mg IM single dose (746). When considering these alternative regimens, the addition of metronidazole should be considered to provide anaerobic coverage. No data have been published regarding the use of oral cephalosporins for the treatment of PID. As a result of the emergence of quinolone-resistant *N. gonorrhoeae*, regimens that include a quinolone agent are no longer routinely recommended for the treatment of PID. If allergy precludes the use of cephalosporin therapy, if the community prevalence and individual risk for gonorrhea are low, and if follow-up is likely, use of fluoroquinolones for 14 days (levofloxacin 500 mg orally once daily, ofloxacin 400 mg twice daily, or moxifloxacin 400 mg orally once daily) with metronidazole for 14 days (500 mg orally twice daily) can be considered (747–749). Diagnostic tests for gonorrhea must be obtained before instituting therapy, and persons should be managed as follows.

- If the culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility testing.
- If the isolate is determined to be quinolone-resistant *N. gonorrhoeae* (QRNG) or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), consultation with an infectious-disease specialist is recommended.

Other Management Considerations

To minimize disease transmission, women should be instructed to abstain from sexual intercourse until therapy is completed, symptoms have resolved, and sex partners have been adequately treated (See chlamydia and gonorrhea sections). All women who received a diagnosis of acute PID should be tested for HIV, as well as GC and chlamydia, using NAAT.

Follow-Up

Women should demonstrate clinical improvement (e.g., defervescence; reduction in direct or rebound abdominal tenderness; and reduction in uterine, adnexal, and cervical motion tenderness) within 3 days after initiation of therapy. If no clinical improvement has occurred within 72 hours after outpatient IM/oral therapy, hospitalization, assessment of the antimicrobial regimen, and additional diagnostics (including consideration of diagnostic laparoscopy for alternative diagnoses) are recommended. All women who have received a diagnosis of chlamydial or gonococcal PID should be retested 3 months after treatment, regardless of whether their sex partners were treated (480). If retesting at 3 months is not possible, these women should be retested whenever they next present for medical care in the 12 months following treatment.

Management of Sex Partners

Men who have had sexual contact with a woman with PID during the 60 days preceding her onset of symptoms should be evaluated, tested, and presumptively treated for chlamydia and gonorrhea, regardless of the etiology of PID or pathogens isolated from the woman. If a woman's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Male partners of women who have PID caused by *C. trachomatis* and/or *N. gonorrhoeae* frequently are asymptomatic. Arrangements should be made to link male partners to care. If linkage is delayed or unlikely, EPT and enhanced referral are alternative approaches to treating male partners of women who have chlamydia or gonococcal infections (see Partner Services) (93,94). Partners should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., until therapy is completed and symptoms have resolved, if originally present).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

The cross reactivity between penicillins and cephalosporins is <2.5% in persons with a history of penicillin allergy (428–431,464). The risk for penicillin cross-reactivity is highest with first-generation cephalosporins, but is negligible between most second-generation (cefotaxime) and all third-generation (ceftriaxone) cephalosporins (428–431) (see Management of Persons who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women suspected to have PID are at high risk for maternal morbidity and preterm delivery. These women should be hospitalized and treated with intravenous antibiotics.

HIV Infection

Differences in the clinical manifestations of PID between women with HIV infection and women without HIV infection have not been well delineated. In early observational studies, women with HIV infection and PID were more likely to require surgical intervention. More comprehensive observational and controlled studies have demonstrated that women with HIV infection and PID have similar symptoms when compared with HIV-negative women with PID (266,750,751), except they are more likely to have a tubo-ovarian abscess; women with HIV infection responded equally well to recommended parenteral and IM/oral antibiotic regimens as women without HIV infection. The microbiologic findings for women with HIV infection and women without HIV infection were

similar, except women with HIV infection had higher rates of concomitant *M. hominis* and streptococcal infections. These data are insufficient for determining whether women with HIV infection and PID require more aggressive management (e.g., hospitalization or intravenous antimicrobial regimens).

Intrauterine Contraceptive Devices

IUDs are one of the most effective contraceptive methods. Copper-containing and levonorgestrel-releasing IUDs are available in the United States. The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion (752,753). If an IUD user receives a diagnosis of PID, the IUD does not need to be removed (63). However, the woman should receive treatment according to these recommendations and should have close clinical follow-up. If no clinical improvement occurs within 48–72 hours of initiating treatment, providers should consider removing the IUD. A systematic review of evidence found that treatment outcomes did not generally differ between women with PID who retained the IUD and those who had the IUD removed (754). These studies primarily included women using copper or other nonhormonal IUDs. No studies are available regarding treatment outcomes in women using levonorgestrel-releasing IUDs.

Epididymitis

Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts <6 weeks (755). Sometimes the testis is also involved—a condition referred to as epididymo-orchitis. A high index of suspicion for spermatic cord (testicular) torsion must be maintained in men who present with a sudden onset of symptoms associated with epididymitis, as this condition is a surgical emergency.

Among sexually active men aged <35 years, acute epididymitis is most frequently caused by *C. trachomatis* or *N. gonorrhoeae*. Acute epididymitis caused by sexually transmitted enteric organisms (e.g., *Escherichia coli*) also occurs among men who are the insertive partner during anal intercourse. Sexually transmitted acute epididymitis usually is accompanied by urethritis, which frequently is asymptomatic. Other nonsexually transmitted infectious causes of acute epididymitis (e.g., Fournier's gangrene) are uncommon and should be managed in consultation with a urologist.

In men aged ≥35 years who do not report insertive anal intercourse, sexually transmitted acute epididymitis is less common. In this group, the epididymis usually becomes infected in the setting of bacteriuria secondary to bladder outlet obstruction (e.g., benign prostatic hyperplasia) (756). In older men, nonsexually transmitted acute epididymitis is also

associated with prostate biopsy, urinary tract instrumentation or surgery, systemic disease, and/or immunosuppression.

Chronic epididymitis is characterized by a ≥ 6 week history of symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis. Chronic infectious epididymitis is most frequently seen in conditions associated with a granulomatous reaction; *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis and should be suspected, especially in men with a known history of or recent exposure to TB. The differential diagnosis of chronic non-infectious epididymitis, sometimes termed “orchalgia/epididymalgia” is broad (i.e., trauma, cancer, autoimmune, and idiopathic conditions); men with this diagnosis should be referred to a urologist for clinical management (755,757).

Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness, hydrocele, and palpable swelling of the epididymis. Although inflammation and swelling usually begins in the tail of the epididymis, it can spread to involve the rest of the epididymis and testicle. The spermatic cord is usually tender and swollen. Spermatic cord (testicular) torsion, a surgical emergency, should be considered in all cases, but it occurs more frequently among adolescents and in men without evidence of inflammation or infection. In men with severe, unilateral pain with sudden onset, those whose test results do not support a diagnosis of urethritis or urinary-tract infection, or men in whom diagnosis of acute epididymitis is questionable, immediate referral to a urologist for evaluation of testicular torsion is important because testicular viability might be compromised.

Bilateral symptoms should raise suspicion of other causes of testicular pain. Radionuclide scanning of the scrotum is the most accurate method to diagnose epididymitis, but it is not routinely available. Ultrasound should be primarily used for ruling out torsion of the spermatic cord in cases of acute, unilateral, painful scrotum swelling. However, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound, when torsion is not ruled out by ultrasound, differentiation between spermatic cord torsion and epididymitis must be made on the basis of clinical evaluation. Although ultrasound can demonstrate epididymal hyperemia and swelling associated with epididymitis, it provides minimal utility for men with a clinical presentation consistent with epididymitis, because a negative ultrasound does not alter clinical management. Ultrasound should be reserved for men with scrotal pain who cannot receive an accurate diagnosis by history, physical examination, and objective laboratory findings or if torsion of the spermatic cord is suspected.

All suspected cases of acute epididymitis should be evaluated for objective evidence of inflammation by one of the following point-of-care tests.

- Gram or methylene blue or gentian violet (MB/GV) stain of urethral secretions demonstrating ≥ 2 WBC per oil immersion field (478). These stains are preferred point-of-care diagnostic tests for evaluating urethritis because they are highly sensitive and specific for documenting both urethral inflammation and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC-containing intracellular Gram-negative or purple diplococci on urethral Gram stain or MB/GV smear, respectively.
- Positive leukocyte esterase test on first-void urine.
- Microscopic examination of sediment from a spun first-void urine demonstrating ≥ 10 WBC per high power field.

All suspected cases of acute epididymitis should be tested for *C. trachomatis* and for *N. gonorrhoeae* by NAAT. Urine is the preferred specimen for NAAT testing in men (394). Urine cultures for chlamydia and gonococcal epididymitis are insensitive and are not recommended. Urine bacterial culture might have a higher yield in men with sexually transmitted enteric infections and in older men with acute epididymitis caused by genitourinary bacteriuria.

Treatment

To prevent complications and transmission of sexually transmitted infections, presumptive therapy is indicated at the time of the visit before all laboratory test results are available. Selection of presumptive therapy is based on risk for chlamydia and gonorrhea and/or enteric organisms. The goals of treatment of acute epididymitis are 1) microbiologic cure of infection, 2) improvement of signs and symptoms, 3) prevention of transmission of chlamydia and gonorrhea to others, and 4) a decrease in potential chlamydia/gonorrhea epididymitis complications (e.g., infertility and chronic pain). Although most men with acute epididymitis can be treated on an outpatient basis, referral to a specialist and hospitalization should be considered when severe pain or fever suggests other diagnoses (e.g., torsion, testicular infarction, abscess, and necrotizing fasciitis) or when men are unable to comply with an antimicrobial regimen. Because high fever is uncommon and indicates a complicated infection, hospitalization for further evaluation is recommended.

Recommended Regimens

For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea

Ceftriaxone 250 mg IM in a single dose

PLUS

Doxycycline 100 mg orally twice a day for 10 days

For acute epididymitis most likely caused by sexually-transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex)

Ceftriaxone 250 mg IM in a single dose

PLUS

Levofloxacin 500 mg orally once a day for 10 days

OR

Ofloxacin 300 mg orally twice a day for 10 days

For acute epididymitis most likely caused by enteric organisms

Levofloxacin 500 mg orally once daily for 10 days

OR

Ofloxacin 300 mg orally twice a day for 10 days

Therapy including levofloxacin or ofloxacin should be considered if the infection is most likely caused by enteric organisms and gonorrhea has been ruled out by gram, MB, or GV stain. This includes men who have undergone prostate biopsy, vasectomy, and other urinary-tract instrumentation procedures. As an adjunct to therapy, bed rest, scrotal elevation, and nonsteroidal anti-inflammatory drugs are recommended until fever and local inflammation have subsided. Complete resolution of discomfort might not occur until a few weeks after completion of the antibiotic regimen.

Other Management Considerations

Men who have acute epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be advised to abstain from sexual intercourse until they and their partners have been adequately treated and symptoms have resolved. All men with acute epididymitis should be tested for other STDs, including HIV.

Follow-Up

Men should be instructed to return to their health-care providers if their symptoms fail to improve within 72 hours of the initiation of treatment. Signs and symptoms of epididymitis that do not subside within 3 days require re-evaluation of the diagnosis and therapy. Men who experience swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated for alternative diagnoses, including tumor, abscess, infarction, testicular cancer, tuberculosis, and fungal epididymitis.

Management of Sex Partners

Men who have acute sexually transmitted epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer for evaluation, testing, and presumptive treatment all sex partners with whom they have had sexual contact within the 60 days preceding onset of symptoms (see Chlamydial Infections and Gonorrheal Infections). If the last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Arrangements should be made to link female partners to care. EPT and enhanced referral (see Partner Services) are effective strategies for treating female sex partners of men who have chlamydia or gonorrhea for whom linkage to care is anticipated to be delayed (93,94). Partners should be instructed to abstain from sexual intercourse until they and their sex partners are adequately treated and symptoms have resolved.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

The cross reactivity between penicillins and cephalosporins is <2.5% in persons with a history of penicillin allergy (428–431,464). The risk for penicillin cross-reactivity is highest with first-generation cephalosporins, but is negligible between most second-generation (cefotaxime) and all third-generation (ceftriaxone) cephalosporins (428–431) (see Management of Persons with a History of Penicillin Allergy). Alternative regimens have not been studied; therefore, clinicians should consult infectious-disease specialists if such regimens are required.

HIV Infection

Men with HIV infection who have uncomplicated acute epididymitis should receive the same treatment regimen as those who are HIV negative. Other etiologic agents have been implicated in acute epididymitis in men with HIV infection, including CMV, salmonella, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium* sp., *Mycoplasma* sp., and *Mima polymorpha*. Fungi and mycobacteria also are more likely to cause acute epididymitis in men with HIV infection than in those who are immunocompetent.



Mindful

Continuing Education

"This course was developed from the public domain document: Sexually Transmitted Diseases Treatment Guidelines, 2015 – Centers for Disease Control and Prevention (CDC) and the Morbidity and Mortality Weekly Report (MMWR)."