

treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing.

All persons found to have who have gonorrhea also should be tested for other STDs, including chlamydia, syphilis, and HIV.

Dual Therapy for Gonococcal and Chlamydial Infections

Patients infected with *N. gonorrhoeae* frequently are coinfecting with *C. trachomatis*; this finding has led to the recommendation that patients treated for gonococcal infection also be treated routinely with a regimen that is effective against uncomplicated genital *C. trachomatis* infection (294). Because most gonococci in the United States are susceptible to doxycycline and azithromycin, routine cotreatment might also hinder the development of antimicrobial-resistant *N. gonorrhoeae*. Limited data suggest that dual treatment with azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins (295,296).

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies (297). Quinolone-resistant *N. gonorrhoeae* strains are now widely disseminated throughout the United States and the world (298). As of April 2007, quinolones are no longer recommended in the United States for the treatment of gonorrhea and associated conditions, such as PID (299). Consequently, only one class of antimicrobials, the cephalosporins, is recommended and available for the treatment of gonorrhea in the United States. The CDC website (<http://www.cdc.gov/std/gisp>) and state health departments can provide the most current information.

The proportion of isolates in CDC's Gonococcal Isolate Surveillance Project (GISP) demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low over time; during 1987–2008, only four isolates were found to have decreased susceptibility to ceftriaxone, and 48 isolates had decreased susceptibility to cefixime. In 2008, no isolates demonstrated decreased susceptibility to ceftriaxone; cefixime was not part of test panel during that year (93). Although only two cases of suspected treatment failure with ceftriaxone have been reported (300), approximately 50 patients are thought to have failed oral cephalosporin treatment (301–304).

Most of the treatment failures resulting from use of oral cephalosporins have been reported from Asian countries, although one possible case was reported in Hawaii in 2001 (305). To ensure appropriate antibiotic therapy, clinicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries.

Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (297). GISP, which samples approximately 3% of all U.S. men who have gonococcal infections, is a mainstay of surveillance. However, surveillance by clinicians also is critical. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should perform culture and susceptibility testing of relevant clinical specimens, consult a specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities. Health departments should prioritize partner notification and contact tracing of patients with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or associated with patients whose isolates demonstrate decreased susceptibility to cephalosporin.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

OR, IF NOT AN OPTION

Cefixime 400 mg orally in a single dose

OR

Single-dose injectible **cephalosporin** regimens

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

To maximize compliance with recommended therapies, medications for gonococcal infections should be dispensed on site. 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 published clinical trials (306,307). A 250-mg dose of ceftriaxone is now recommended over a 125-mg dose given the 1) increasingly wide geographic distribution of isolates demonstrating decreased susceptibility to cephalosporins in vitro, 2) reports of ceftriaxone treatment failures, 3) improved efficacy of ceftriaxone 250 mg in pharyngeal infection (which is often unrecognized), and 4) the utility of having a simple and consistent recommendation for treatment regardless of the anatomic site involved.

A 400-mg oral dose of cefixime does not provide as high, nor as sustained, a bactericidal level as that provided by the 250-mg dose of ceftriaxone. In published clinical trials, the 400-mg dose cured 97.5% of uncomplicated urogenital and anorectal (95% CI = 95.4%–99.8%) and 92.3% of pharyngeal gonococcal infections (95% CI = 74.9%–99.1%) (306,307). Although cefixime can be administered orally, this advantage is offset by the limited efficacy of cefixime (as well as other oral cephalosporins) for treating gonococcal infections of the pharynx. Providers should inquire about oral sexual exposure and if reported, treat these patients with ceftriaxone because of this drug's well documented efficacy in treating pharyngeal infection.

Single-dose injectible cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and highly effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime (500 mg, administered IM), cefoxitin (2 g, administered IM with probenecid 1 g orally), and cefotaxime (500 mg, administered IM). None of the injectible cephalosporins offer any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain (306,307).

Alternative Regimens

Several other antimicrobials are active against *N. gonorrhoeae*, but none have substantial advantages over the recommended regimens, and they should not be used if pharyngeal infection is suspected. Some evidence suggests that cefpodoxime 400-mg orally can be considered an alternative in the treatment of uncomplicated urogenital gonorrhea; this regimen meets the minimum efficacy criteria for alternative regimens for urogenital infection (demonstrated efficacy of $\geq 95\%$ in clinical trials with lower 95% CI of $>90\%$) (307). In one clinical trial, cefpodoxime 400 mg orally was found to have a urogenital and rectal cure rate of 96.6% (95% CI = 93.9%), but the efficacy of cefpodoxime 400 mg orally at the pharyngeal site was poor (70.3%, 95% CI = 53.0%) (Hall, unpublished data, 2010). Gonococcal strains with decreased susceptibility to oral cephalosporins have been reported in the United States (308). With a cure rate of 96.5% (95% CI = 93.6%–98.3%) for urogenital and rectal infection, cefpodoxime proxetil 200 mg orally meets the criteria for an alternative regimen; however, its use is not advised because of concerns about the pharmacodynamics of cefpodoxime using this dose. Efficacy in treating pharyngeal infection with cefpodoxime 200 mg is unsatisfactory (78.9%; 95% CI = 54.5%–94%), as with cefpodoxime at the 400-mg dose.

Treatment with cefuroxime axetil 1 g orally meets the criteria for minimum efficacy as an alternative regimen for urogenital and rectal infection (95.9%; 95% CI = 94.3%–97.2%), but the pharmacodynamics of cefuroxime axetil 1 g orally are

less favorable than those of cefpodoxime 400 mg, cefixime 400 mg, or ceftriaxone 125 mg (309). The efficacy of cefuroxime axetil 1 g orally in treating pharyngeal infection is poor (56.9%; 95% CI = 42.2%–70.7%).

Spectinomycin, which is useful in persons who cannot tolerate cephalosporins, is expensive, must be injected, and is not available in the United States (updates available at: www.cdc.gov/std/treatment) (310). However, it has been effective in published clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections. Spectinomycin has poor efficacy against pharyngeal infection (51.8%; 95% CI = 38.7%–64.9%) (306).

Azithromycin 2 g orally is effective against uncomplicated gonococcal infection (99.2%; 95% CI = 97.3%–99.9%), but concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides should restrict its use to limited circumstances. Although azithromycin 1 g meets alternative regimen criteria (97.6%; 95% CI = 95.7%–98.9%), it is not recommended because several studies have documented treatment failures, and concerns about possible rapid emergence of antimicrobial resistance with the 1-g dose of azithromycin are even greater than with the 2-g dose (311–313). *N. gonorrhoeae* in the United States is not adequately susceptible to penicillins, tetracyclines, and older macrolides (e.g., erythromycin) for these antimicrobials to be recommended.

Uncomplicated Gonococcal Infections of the Pharynx

Most gonococcal infections of the pharynx are asymptomatic and can be relatively common in some populations (103,278,279,314). Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites (315). Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure $>90\%$ of gonococcal pharyngeal infections (306,307). Providers should ask their patients about oral sexual exposure; if reported, patients should be treated with a regimen with acceptable efficacy against pharyngeal infection. Chlamydial coinfection of the pharynx is unusual; however, because coinfection at genital sites sometimes occurs, treatment for both gonorrhea and chlamydia is recommended.

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose

PLUS

Azithromycin 1g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

stain is not available, clinical criteria can be used and require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- presence of clue cells 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 (320). Other tests, including a DNA probe-based test for high concentrations of *G. vaginalis* (Affirm VP III, Becton Dickinson, Sparks, Maryland), a prolineaminopeptidase test card (Pip Activity TestCard, Quidel, San Diego, California), and the OSOM BVBlue test have acceptable performance characteristics compared with Gram stain. Although a card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR also has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is uncertain. Detection of one organism or group of organisms might be predictive of BV by Gram stain (321). However, additional evaluations are needed to confirm these associations. 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.

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* or *N. gonorrhoeae* (322), HIV, and other viral STDs.

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†

* Consuming alcohol should be avoided during treatment and for 24 hours thereafter.

† 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).

Providers should consider patient preference, possible side-effects, drug interactions, and other coinfections when selecting a regimen. Women should be advised to refrain from intercourse or to 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

Alternative regimens include several tinidazole regimens (323) or clindamycin (oral or intravaginal) (324). Additional regimens include metronidazole (750-mg extended release tablets once daily for 7 days), or a single dose of clindamycin intravaginal cream, although data on the performance of these alternative regimens are limited.

Several studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV and restore normal flora (325–327). Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because recurrence of BV is common, women should be advised to return for evaluation if symptoms recur. Detection of certain BV-associated organisms have been associated with antimicrobial resistance and might determine risk for subsequent treatment failure (328–333). Limited data are available regarding optimal management strategies for women with early treatment failure. Using a different treatment regimen might be an option in patients who have a recurrence; however, re-treatment with the same topical regimen is another acceptable approach for treating recurrent BV during the early stages of infection (334). For women with multiple recurrences after completion of a recommended regimen, 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 (335). Limited data suggest that oral nitroimidazole followed by intravaginal boric acid and suppressive metronidazole gel for those women in remission might be an option in women with recurrent BV (336). Monthly oral metronidazole administered with fluconazole has also been evaluated as suppressive therapy (337).