DUAL THERAPY FOR GONOCOCCAL INFECTIONS

ABSTRACT: Gonorrhea is the second most commonly reported bacterial sexually transmitted disease in the United States, with an estimated 820,000 new Neisseria gonorrhoeae infections occurring each year. Antimicrobial resistance limits treatment success, heightens the risk of complications, and may facilitate the transmission of sexually transmitted infections. Neisseria gonorrhoeae has developed resistance to the sulfonamides, the tetracyclines, and penicillin. Dual therapy with ceftriaxone and azithromycin remains the only recommended first-line regimen for the treatment of gonorrhea in the United States. Dual therapy with ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously, and under direct observation. Pregnant women who are infected with N gonorrhoeae should be treated with the recommended dual therapy. A test-of-cure is not needed for individuals diagnosed with uncomplicated urogenital or rectal gonorrhea who are treated with the recommended or alternative regimens. Repeat N gonorrhoeae infection is prevalent among patients who have been diagnosed with and treated for gonorrhea in the preceding several months. Most of these infections result from reinfection; therefore, clinicians should advise patients with gonorrhea to be retested 3 months after treatment. Pregnant women with antenatal gonococcal infection should be retested in the third trimester unless recently treated.

Recommendations

Based on the following information, the American College of Obstetricians and Gynecologists makes these recommendations:

• Dual therapy with ceftriaxone and azithromycin should be administered. It should be administered together on the same day, preferably simultaneously, and under direct observation.
• Test-of-cure is not recommended for women diagnosed with uncomplicated urogenital or rectal gonorrhea treated with the recommended or alternative regimens.
• Pregnant women treated with dual therapy for gonorrhea do not require a test-of-cure.
• Women with pharyngeal gonorrhea treated with an alternative regimen should return 14 days after treatment for a test-of-cure using either culture or nucleic acid amplification test (NAAT).
• The Centers for Disease Control and Prevention’s (CDC) guidance (www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm?s_cid=rr6403a1_e) on the treatment of gonococcal infections is likely to evolve in the coming years, and obstetrician–gynecologists should remain aware of new developments in this area. The CDC web site (www.cdc.gov/std/gisp/) and state health departments can provide the most current information on gonococcal susceptibility.

Gonorrhea is the second most commonly reported bacterial sexually transmitted disease (STD) in the United States, with an estimated 820,000 new Neisseria gonorrhoeae infections occurring each year (1). Antimicrobial resistance limits treatment success, heightens the risk of complications, and may facilitate the transmission of sexually transmitted infections (STIs). Neisseria gonorrhoeae has developed resistance to sulfonamides, tetracyclines, and penicillin. In 2007, emergence of fluoroquinolone-resistant N gonorrhoeae prompted the CDC to no longer recommend fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining class of recommended antimicrobials (2).

In an attempt to prevent development of resistance to cephalosporins, the CDC’s 2010 STD treatment...
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guidelines recommended combination therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline, even if NAAT for Chlamydia trachomatis was negative at the time of treatment (3). This emerging cephalosporin resistance was manifested from 2006 to 2011, when the minimum inhibitory concentrations of cefixime needed to inhibit the growth in vitro of N. gonorrhoeae strains in the United States increased, suggesting that the effectiveness of cefixime might be waning (4, 5). As a result, cefixime is no longer a first-line regimen. Dual therapy with ceftriaxone and azithromycin remains the only recommended first-line regimen for the treatment of gonorrhea in the United States (1, 5).

Treatment Regimens

Dual therapy with ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously, and under direct observation (see Box 1). Ceftriaxone in a single-intramuscular (IM) injection of 250 mg provides sustained, high bactericidal levels in the blood; clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing more than 98% of all infections (6, 7). The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and adherence advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin (1, 8). The use of ceftriaxone or cefixime is contraindicated in those patients with a history of an IgE mediated β-lactam allergy, such as anaphylaxis, Stevens–Johnson syndrome, or toxic epidermal necrolysis (see Box 1 for alternate treatment regimens) (9, 10).

Recent clinical trials showed that dual treatment with a single 320-mg dose of oral gemifloxacin plus a 2-g dose of oral azithromycin, or dual treatment with a single 240-mg dose of IM gentamicin plus a 2-g dose of oral azithromycin, were effective for uncomplicated urogenital gonorrhea (11). Either of these regimens may be considered as alternative treatment options when ceftriaxone is contraindicated. Monotherapy with a 2-g dose of oral azithromycin as a single dose in women who are not pregnant is no longer recommended in the United States (12–16).

Pregnancy

Pregnant women who are infected with N. gonorrhoeae should be treated with the recommended dual therapy. A test-of-cure is not needed for individuals diagnosed with uncomplicated urogenital or rectal gonorrhea who are treated with the recommended or alternative regimen. Patients with severe penicillin or cephalosporin allergy can be administered dual therapy with a 240-mg dose of IM gentamicin and 2-g oral azithromycin. The use of gentamicin to treat chorioamnionitis demonstrates its safety in pregnancy (17, 18). Based on expert opinion, another alternative is a 2-g single dose of oral azithromycin in patients who are allergic to gentamicin and cephalosporins, but this category of patients need a test-of-cure 1 week after treatment. Such patients also may be referred to an infectious disease specialist. Dual therapy with ceftriaxone and azithromycin is recommended if the patient has a history of rash without anaphylaxis manifestations. Neither doxycycline nor quinolones are recommended during pregnancy.

Human Immunodeficiency Virus Infection

Patients infected with human immunodeficiency virus (HIV) with gonococcal infection should receive the same recommended dual therapy as those who do not have HIV (1). See general treatment recommendations described under “Treatment Regimens.”

Management of Sex Partners

Recent sex partners within 60 days of diagnosis should be encouraged to seek evaluation and presumptive treatment for N. gonorrhoeae and C. trachomatis infections.

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**Box 1. Recommended Antibiotic Regimens for Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum**

**Preferred Regimen (First Line)**
- Ceftriaxone, 250 mg, single-intramuscular dose
- Azithromycin, 1 g, single-oral dose*

**Alternative Regimens (Second Line)**
- If ceftriaxone is not available
  - Cefixime, 400 mg, single-oral dose
  - Azithromycin, 1 g, single-oral dose*
- If the patient has a severe penicillin allergy
  - Gemifloxacin, 320 mg, single-oral dose
  - Azithromycin, 2 g, single-oral dose
  - Gentamicin, 240 mg, single-intramuscular dose
- Azithromycin, 2 g, single-oral dose*

*If azithromycin is not available or if the patient is allergic to azithromycin, doxycycline (100 mg orally twice a day for 7 days) may be substituted as the second antimicrobial.

Note the following:
- Dose of azithromycin is increased to 2 g when used with the alternative antibiotics, gemifloxacin or gentamicin.
- Dual therapy with gentamicin and azithromycin or azithromycin alone should be used during pregnancy.
If the last potential exposure was greater than 60 days, the most recent sex partner should be treated. Patients and sex partners should abstain from sexual activity for 7 days after treatment and until sex partners are adequately treated. If an obstetrician–gynecologist or other health care provider cannot ensure that an infected patient’s partner will be promptly linked to care, and where legally accepted, expedited partner therapy with cefixime (400 mg) and azithromycin (1 g) should be delivered to the partner by the patient, a disease investigation specialist, or through a collaborating pharmacy. The CDC maintains a web site with information about the legal status of expedited partner therapy in all 50 states and other jurisdictions; additional information is available from the Guttmacher Institute. More information on expedited partner therapy is available in the American College of Obstetricians and Gynecologists’ Committee Opinion Number 632, Expedited Partner Therapy in the Management of Gonorrhea and Chlamydial Infection. Expedited partner therapy should be accompanied by written materials educating partners about their exposure to gonorrhea, the importance of therapy, and when to seek clinical evaluation for reactions or complications.

Retesting
Appropriately treated patients do not need a test-of-cure. Retesting to detect repeat infection is distinct from test-of-cure to detect therapeutic failure. For patients who get retested and receive positive test results, most are more likely to be from reinfection than from treatment failure. Such patients should be retreated with the recommended dual regimen (250 mg of ceftriaxone IM plus 1 g of azithromycin orally). Patients who have symptoms that persist after treatment should be evaluated by culture for N gonorrhoeae (preferably with simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by C trachomatis or other organisms.

Suspected Cephalosporin Treatment Failure
Cephalosporin treatment failure is defined as the persistence of N gonorrhoeae infection despite appropriate cephalosporin treatment and is indicative of infection with cephalosporin-resistant gonorrhea in individuals whose partners were adequately treated and whose risk of reinfection is low. Suspected treatment failure has been reported among individuals receiving oral and injectable cephalosporins. Treatment failure should be considered in individuals whose symptoms do not resolve within 3–5 days after appropriate treatment and who report no sexual contact during the posttreatment follow-up period, and in individuals with a positive test-of-cure (eg, a positive culture after more than 72 hours or a positive NAAT result 7 or more days after receiving recommended treatment) and who report no sexual contact during the posttreatment follow-up period. Treatment failure also should be considered in individuals who have a positive culture on test-of-cure (if obtained) and there is evidence of decreased susceptibility to cephalosporins on antimicrobial susceptibility testing, regardless of whether sexual contact is reported during the posttreatment follow-up period.

In cases where reinfection is unlikely and treatment failure is suspected, before retreatment of the individual, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing should be performed if N gonorrhoeae is isolated. All isolates should be sent to the CDC for antimicrobial susceptibility testing; local laboratories should store isolates for possible further testing if needed. Instructions for shipping isolates to CDC can be found at www.cdc.gov/std/gonorrhea/arg/specimen_shipping_instructions1-29-08.pdf.

For individuals with suspected cephalosporin treatment failure, the treating clinician should consult an infectious disease specialist, an STD/HIV Prevention Training Center clinical expert (www.nnptc.org), the local or state health department STD program, or the CDC for advice. Dual treatment with a single 320-mg dose of oral gemifloxacin plus a 2-g dose of oral azithromycin or dual treatment with a single 240-mg dose of gentamicin IM plus a 2-g dose of oral azithromycin may be considered, particularly when isolates are found to have elevated cephalosporin minimum inhibitory concentrations. Individuals with suspected treatment failure after treatment with the alternative regimen (ceftriaxone and azithromycin) should be treated with a single 250-mg IM dose of ceftriaxone and a single 2-g oral dose of azithromycin. 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. Obstetrician–gynecologists or other health care providers should encourage the patient’s sex partners from the preceding 60 days to seek prompt evaluation with culture and presumptive treatment using the same regimen used for the patient.

Follow-Up
Repeat N gonorrhoeae infection is prevalent among patients who have been diagnosed with and treated for gonorrhea in the preceding several months. Most of these infections result from reinfection and clinicians should therefore advise patients with gonorrhea to be retested 3 months after treatment. If patients do not seek medical care for retesting in 3 months, obstetrician–gynecologists or other health care providers are encouraged to test these patients whenever they next seek medical care within the following 12 months, regardless of whether the patients believe that their sex partners were treated. Pregnant women with antenatal gonococcal infection should be retested in the third trimester unless recently treated.
References


