

CDC Updates Gonococcal Guidelines

Sexually transmitted gonococcal infections are a major cause of morbidity among sexually-active individuals, and rates of infection in the U.S. have increased by 63% since 2014.¹ In 2010, the Centers for Disease Control and Prevention (CDC) recommended combination therapy with a single dose of intramuscular (IM) ceftriaxone 250mg plus oral azithromycin 1g for treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum as a strategy to prevent ceftriaxone resistance and treat possible coinfection with *Chlamydia trachomatis*.² However, growing concerns for antimicrobial stewardship-related collateral damage as well as increasing resistance rates to first-line agents have led to updated recommendations. This newsletter reviews the updated guideline recommendations for the treatment of gonococcal infections and highlights considerations for implementation at DASON community hospitals.³

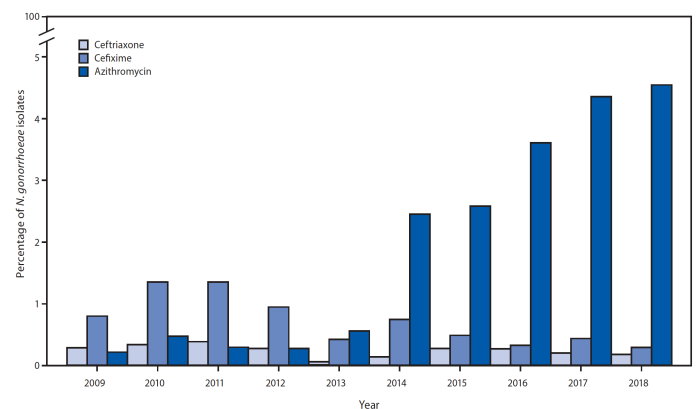
What's New in the 2020 Guidelines?

First, higher doses of ceftriaxone are now recommended due to concerns regarding rising gonococcal minimum inhibitory concentrations (MICs) worldwide. The updated guidelines recommend weight-based ceftriaxone dosing regimens of 500mg (if < 150kg) or 1g (if > 150kg) administered intramuscularly (IM). These new high-dose ceftriaxone dosing regimens are supported by pharmacokinetic (PK) and pharmacodynamic (PD) data in murine models suggesting lower doses of ceftriaxone do not reliably achieve rapid and sustained concentrations higher than the MIC > 0.25mcg/mL at the site of infection for an extended duration.^{4,5}

Second, combination therapy (e.g., ceftriaxone plus azithromycin) directed against *N. gonorrhoea* is no longer recommended based on the following rationale: 1) increasing concerns for antimicrobial resistance and the potential impact on commensal organisms and concurrent pathogens; 2) continued low rates of

ceftriaxone resistance and low rates of ceftriaxone-based regimen treatment failures; and 3) increasing rates of azithromycin resistance.⁶ **Figure 1** shows the percentage of *N. gonorrhoea* isolates with elevated MICs to ceftriaxone, cefixime, and azithromycin from 2009 - 2018.¹ In the latest guidelines, high-dose ceftriaxone monotherapy is recommended so long as chlamydial coinfection has been excluded by nucleic acid amplification test. **Table 1** outlines appropriate treatment options recommended in the updated guidelines.

Figure 1. Percentage of *N. gonorrhoea* isolates with elevated MICs to azithromycin, ceftriaxone, and cefixime from 2009 - 2018



Third, in the setting of chlamydial coinfection, azithromycin is no longer recommended as first-line therapy except in the setting of pregnancy. Rather, a 7-day course of oral, twice-daily doxycycline is recommended. This change in therapy is recommended on the basis of large observational studies demonstrating macrolide resistance among *N. gonorrhoeae* and other important pathogens, such as *S. pneumoniae*, in communities receiving mass administration of azithromycin.^{7,8} The latest guidelines do not specifically comment on the safety and efficacy of doxycycline versus azithromycin for treatment of chlamydial infections. However, a meta-analysis published in 2014 demonstrated a pooled efficacy difference in favor of doxycycline of 1.5% to 2.6%.⁹ Of note, the authors of this

meta-analysis call for additional high quality randomized controlled trials to confirm this observation.

Table 1. Latest Recommendations for the Treatment of Gonococcal Infections

Uncomplicated gonococcal infections of the <u>cervix</u>, <u>urethra</u>, or <u>rectum</u>:
<p>First-line:</p> <ul style="list-style-type: none"> • ceftriaxone 500mg IM x 1 (< 150kg) • ceftriaxone 1g IM x 1 (≥ 150kg) • if chlamydial coinfection, add: <ul style="list-style-type: none"> ○ doxycycline 100mg PO BID x 7d <u>OR</u> ○ azithromycin 1g PO x 1 (pregnant)
<p>Alternatives:</p> <ul style="list-style-type: none"> • gentamicin 240mg IM <u>PLUS</u> azithromycin 2g PO x 1 • cefixime 800mg PO x 1 • if chlamydial coinfection and cefixime used for treatment, add: <ul style="list-style-type: none"> ○ doxycycline 100mg PO BID x 7d <u>OR</u> ○ azithromycin 1g PO x 1 (pregnant)
Uncomplicated gonococcal infections of the <u>pharynx</u>:
<p>First-line:</p> <ul style="list-style-type: none"> • ceftriaxone 500mg IM x 1 (< 150kg) • ceftriaxone 1g IM x 1 (≥ 150kg) • if chlamydial coinfection, add: <ul style="list-style-type: none"> ○ doxycycline 100mg PO BID x 7d <u>OR</u> ○ azithromycin 1g PO x 1 (pregnant)
<p>Alternatives:</p> <ul style="list-style-type: none"> • no reliable alternatives are available for pharyngeal gonorrhea • if history of severe beta-lactam allergy, perform a thorough assessment of the reaction/allergy history • for persons with anaphylaxis or other severe reactions (e.g., Stevens Johnson) to ceftriaxone, consult an ID specialist

Considerations for DASON Community Hospitals

Implementation of these latest guidelines is critical to combat the emerging threat of antimicrobial-resistant gonorrhea. However, there are several key considerations for implementation that warrant discussion. First, high-dose ceftriaxone regimens will require larger volumes for intramuscular administration. Therefore, it is important to carefully select an appropriate muscle for administration. In adults, the deltoid and thigh can generally tolerate 2 mL, whereas the gluteus maximus can tolerate up to 5 mL.¹⁰ Given the fact that the maximum ceftriaxone concentration recommended for intramuscular injection is 350 mg/mL, the gluteus maximus may be the preferred injection site in most patients, and multiple injection sites may be required if the solution is further diluted with a 1:1 lidocaine 1% solution to reduce pain.¹¹

Another consideration worth noting is patient noncompliance with oral therapy. It is well documented that patients sometimes fail to fill and appropriately take or complete oral medications prescribed in emergency departments.¹² Given the fact that a single dose of oral azithromycin has been replaced with a 7-day course of twice-daily doxycycline, it is important to educate patients on the need to complete therapy and highlight the possible outcomes associated with untreated chlamydial infections.

Summary:

- High-dose intramuscular ceftriaxone regimens of 500mg (< 150 kg) or 1g (≥ 150 kg) are now recommended first-line for the treatment of uncomplicated gonococcal infections
- In adult patients, ceftriaxone 250mg IM for gonococcal infection should be considered a “never event”
- Combination therapy targeting *N. gonorrhoeae* is no longer recommended, so azithromycin should not added for the sole purpose of double coverage
- If chlamydial coinfection is suspected, doxycycline is recommended first-line, whereas azithromycin should be reserved for pregnant patients

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