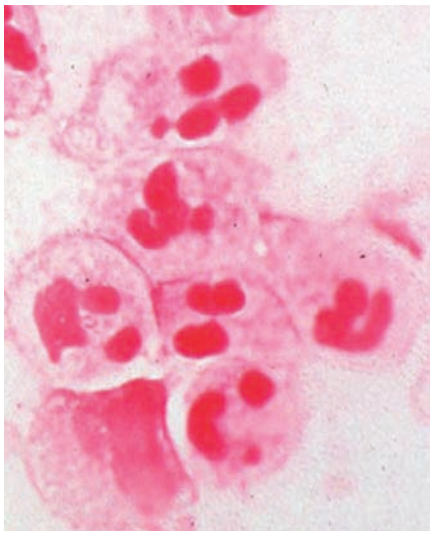
CDC Doubles Dose of Ceftriaxone for Gonorrhea

BY DANIEL MORRAD, DO, JESSICA PESCATORE, DO, & RICHARD PESCATORE, DO



The eyes of scrutiny have once again fallen on how to best treat chlamydia and gonorrhea, two of the most commonly reported communicable diseases in the United States. Such inspection seems warranted because *Neisseria gonorrhoeae* infections have increased by 63 percent and *Chlamydia trachomatis* infections have risen 19 percent since 2014. (CDC. Sexually Transmitted Disease Surveillance 2018; https://bit.ly/2NkvHGJ.)

The sequelae of these sexually transmitted infections (STIs), including pelvic inflammatory disease, ectopic pregnancy, infertility, and increased risk of HIV transmission, are also likely to increase. The Centers for Disease Control and Prevention recently released treatment guidelines for gonococcal infection in response to these rising rates, growing incidence of antibiotic resistance, and emerging data supporting change. (*MMWR Morb Mortal Wkly Rep.* 2020;69[50]:1911; http://bit.ly/3oNajHT.) This approach places antimicrobial stewardship at the forefront of its recommendations and recognizes the importance of definitive therapy at the first contact with the patient.

Perhaps the most significant change in the new recommendations is for a single 500 mg IM dose of ceftriaxone for uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, doubling the dose from 250 mg. Where there is concern for coinfection with *Chlamydia trachomatis* (often the case when urogenital infections are treated empirically in the ED), the CDC recommended adding oral doxycycline 100 mg twice a day for seven days, not the dose or two of azithromycin that much of ED practice has shifted to over the years.

Combination Treatment

Antimicrobial stewardship—the practice of promoting the ideal choice and use of antimicrobials and the dosing, route, and duration of administration to optimize clinical outcomes while minimizing unintended effects—was an apt justification for helping direct the CDC's new regimen. The CDC 2010 gonococcal infection treatment plan combined ceftriaxone with azithromycin, but the 2020 guidelines are pointing away from this regimen based on studies that have shown an increased impact of general antimicrobial use.

A sevenfold increase in reduced susceptibility of *Neisseria gonorrhoeae* to azithromycin with a minimum inhibitory concentration (MIC) of 2.0 µg/mL or higher was seen from 2013 to 2018. (CDC. Sexually Transmitted Disease Surveillance 2018; https://bit.ly/2NkvHGJ.) It's not a resistance relegated to gonorrhea alone: Consistent with recent changes to pneumonia treatment recommendations, investigations on children receiving azithromycin v. placebo and reviews of those taking oral azithromycin for *Streptococcus pneumoniae* infections found both had bacterial biomes with increased resistance to macrolides. The CDC also references other STIs, including *Mycoplasma genitalium* and other enteric pathogens such as *Shigella*, that have displayed increased azithromycin resistance.

Combination treatment for gonorrhea and chlamydia has been the CDC recommendation since the mid-1980s. Fluoroquinolones were ousted in 2007 because of findings by the Gonococcal Isolate Surveillance Project, which showed quinolone-resistant strains of gonorrhea in the United States were taking over the gonococcal microbiome. (*MMWR Morb Mortal Wkly Rep.* 2007;56[14]:332; https://bit.ly/3p1K1BI.)

This pattern of microbial selection left clinicians with intramuscular ceftriaxone or oral cefixime, both cephalosporins, as some of the few outpatient treatment options against gonococcal infections. Unfortunately, by 2012, with the increase of the MIC for cefixime to inhibit growth of *N. gonorrhoeae* in vitro to unreasonable levels, ceftriaxone was left as the only cephalosporin option available.

The recommendation to increase the ceftriaxone dose and drop azithromycin from the treatment plan altogether for uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, should not prevent practitioners from reaching for the more familiar combination in cases of more complicated pathology or diagnostic uncertainty. In some cases, including those of mild pelvic inflammatory disease, therapy with azithromycin (v. doxycycline) and ceftriaxone may still be necessary and more beneficial, particularly if treatment compliance is in question.

Eliminating Uncertainty

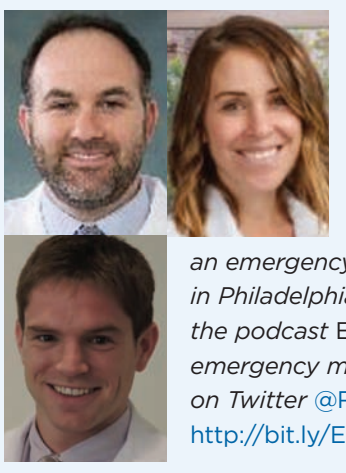
A randomized controlled trial by Savaris, et al., showed that the clinical cure rate for pelvic inflammatory disease treated with ceftriaxone plus azithromycin was 90.3 percent compared with 72.4 percent with doxycycline, suggesting that azithromycin and ceftriaxone may retain a place in the armamentarium. (*Obstet Gynecol*. 2007;110[1]:53.) It's certainly a reasonable option whenever noncompletion of a doxycycline regimen is a consideration.

In addition to removing azithromycin from prior regimens, the CDC now recommends increasing the dose of ceftriaxone from a 250 mg intramuscular dose to 500 mg. This change is based on a number of studies that looked at various ceftriaxone doses that completely eradicated *N. gonorrhoeae* in mice. The optimal dose was 5 mg/kg, translating to a 500 mg dose for the average 80 to 100 kg human; a 250 mg injection was found insufficient for eradicating gonococcal infection.

An added benefit of the increased dose of ceftriaxone is that it will eliminate the uncertainty of treating *N. gonorrhoeae* in the pharynx, an anatomic area where ceftriaxone-based regimens commonly fail. The revised CDC recommendations argue that increasing the dose to a single 500 mg IM shot will maintain ceftriaxone concentrations above the necessary inhibitory levels for longer, an effective treatment for gonococcal pharyngitis.

The revised CDC guidelines now recommend a single 500 IM dose of ceftriaxone for urogenital, rectal, and pharyngeal gonorrhea. A single 1 g IM dose of ceftriaxone should be given to patients weighing more than 150 kg, although such dosing demands consideration of using the intravenous route, which is just as effective as IM administration. (Product information, Genentech USA, Inc.) Adding doxycycline 100 mg orally two times a day for seven days should be the norm in the ED where chlamydial co-infection is rarely excluded.

Azithromycin use now falls outside of these guidelines, but previous literature and experience would continue to support its use when doxycycline completion is dubious. Those with ceftriaxone allergy could receive a single 240 mg IM dose of gentamicin with a single 1 g oral dose of azithromycin. Cefixime can still play a limited role where IM options aren't available, and it can be given as a single 800 mg oral dose, but this offers limited treatment efficacy for pharyngeal gonorrhea. Test-of-cure is not necessary unless treating pharyngeal gonorrhea, and it should be done in seven to 14 days due to decreased efficacy. **EMN**



Clockwise from top left: ***Dr. Morrad*** *is an emergency medicine resident at Einstein Medicine Center Philadelphia.* ***Dr. Jessica Pescatore*** *is an obstetrician/gynecologist with Jefferson Health New Jersey.* ***Dr. Richard Pescatore*** *is the chief physician for the Delaware Division of Public Health and an emergency physician at Einstein Healthcare Network in Philadelphia. He is also the host with Ali Raja, MD, of the podcast* EMN Live*, which focuses on hot topics in emergency medicine:* http://bit.ly/EMNLive*. Follow him on Twitter* @Rick_Pescatore*, and read his past columns at* http://bit.ly/EMN-Pescatore*.*