Hot Topic

National STD Curriculum Podcast

Gonorrhea Treatment Updates

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Season 1, Episode 9

We will review the Update to the CDC's Treatment Guidelines for Gonococcal Infection for 2020 in this episode.

Topics:

- Mgen
- Urethritis
- Gonorrhea
- Neisseria gonorrhoeae
- STD Treatment

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Disclosures

Disclosures for Meena S. Ramchandani, MD

None

References

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Transcript

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In this episode:

[00.00] Introduction
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for

health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

[00.24] Background
In this episode, we'll talk about the new treatment recommendations for *Neisseria gonorrhoeae* that was released in a recent *Morbidity and Mortality Weekly Report* (or *MMWR* for short). This is a big deal as treatment recommendations for uncomplicated gonococcal infections haven't changed since 2015. We'll go through some of the reasons for these new recommendations, as well as two other articles referenced in the *MMWR*.

[00.55] Paper #1

St Cyr S, Barbee L, Workowski KA, Bachmann LH, Pham C, Schlanger K, Torrone E, Weinstock H, Kersh EN, Thorpe P. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep. 2020 Dec 18;69(50):1911-1916. **[PubMed Abstract]**

The first article to discuss was published in December 2020 in the *MMWR* by Dr. St. Cyr and colleagues. And it was titled "Update to CDC's treatment guidelines for gonococcal infection, 2020." And this article is going to be the main focus of this episode. So, I'm going to go over some background, as well as some interesting features of this article that I'd like to point out.

1. The 2015 STD Treatment Guidelines recommended dual therapy for the treatment of gonococcal infections, and this included one dose of ceftriaxone 250 mg intramuscular, as well as either azithromycin 1 gram orally as a single dose or doxycycline 100 mg orally twice a day for seven days.

2. This report updates these previous guidelines and recommends a new treatment for uncomplicated gonococcal infection. This new treatment entails a single dose of ceftriaxone 500 mg that's given intramuscularly alone. If chlamydia infection has not been ruled out, then doxycycline 100 mg twice a day for seven days should be added.

3. So, one of the questions that comes up is, why the shift away from dual therapy for gonorrhea treatment?

- There is an increasing need for antimicrobial stewardship in the public health community as well as patient practice. There's a concern of the potential impact of dual antibiotic therapy on the production of resistance in both commensals and pathogens, as well as the impact of multiple antibiotics on the microbiome on the individual.
- There has been a low incidence of ceftriaxone resistance in *Neisseria gonorrhoeae* isolates that were evaluated by surveillance methods in the U.S. And so, therefore, ceftriaxone alone, but at a higher dose, should be enough to treat this infection.
- Also, the incidence of azithromycin resistance has been increasing over the years. Nationally, the percentage of *Neisseria gonorrhoeae* isolates with reduced susceptibility to azithromycin has increased from 0.6% in 2013 to 4.6% in 2018. This is really concerning and that's a huge increase over time. Among MSM [men who have sex with men], the proportion of surveillance isolates with elevated MIC [minimum inhibitory concentration] value to azithromycin was even higher, at 8.6% in 2018.

4. So, with regards to dosing, the dosing of ceftriaxone has also changed and has been increased. The ceftriaxone dose will increase from 250 mg intramuscularly to 500 mg as an intramuscular injection. For people with gonorrhea who weigh more than 330 lbs., they should actually get 1 gm dose of ceftriaxone. And this recommendation for the increase in the dose of ceftriaxone is due to both pharmacokinetic as well as pharmacodynamic modeling that shows that the optimal antimicrobial dosing for gonorrhea is actually higher than what we have been using so far for the average weight person in the U.S. In addition, ceftriaxone concentrations tend to be more variable in the pharynx, and there have been treatment failures that have

been reported with pharyngeal gonorrhea, and so a higher dose to eradicate this organism is really needed.

5. In the report, the authors note that if chlamydia infection has not been ruled out, then concurrent treatment with doxycycline 100 mg orally for seven days is a preferred treatment over azithromycin. So, why might that be?

- There's increasing evidence that doxycycline might have increased efficacy in clearing chlamydia infection than azithromycin, especially with regards to rectal chlamydia infections.
- Of course, this might depend on the setting in which you see your patients, as well as your specific patient population. So, when the full set of guidelines is released, please take a look for more details on the topic of giving either azithromycin or doxycycline for concurrent chlamydia infection. For example, if I'm taking care of an adolescent or pregnant person, I'd consider giving azithromycin over doxycycline. I'd also consider azithromycin if a patient states a longer course of treatment is just not something they are willing to do.

6. This report recommends that if a patient has pharyngeal gonorrhea, a test-of-cure is recommended at 7 to 14 days after initial treatment, and that's regardless of the regimen used. And I wonder if this might be a challenge to do in clinical practice—to get a patient to return for an oropharyngeal swab and within that short time frame. Personally, if you're going to implement this now, it might be good to err on the side of repeat testing closer to 14 days to potentially avoid false-positive tests. Now, we already do repeat testing for patients with pharyngeal gonorrhea who have been treated with an alternative regimen but getting all our patients with pharyngeal gonorrhea back into clinic for repeat testing in that time frame—well, this might be a challenge in my clinical practice. I think this potential issue underscores the importance of using a more effective 500 mg dose of ceftriaxone. And the recommendation remains for screening for STDs again in three months due to the high rates of reinfection.

7. Lastly, the report also discusses that for pharyngeal gonorrhea, the only good regimen is an intramuscular dose of ceftriaxone at 500 mg. And there really is no reliable alternative treatments that are listed. This already came up for a patient in our clinic who had a severe allergy to cephalosporins, and this presented a dilemma. I guess the first step is to really investigate if the patient has a true severe allergy and then go from there. In these types of situations, the management should be, then, on an individual case basis, and there may be further guidance when the new full STD treatment guideline recommendations from the CDC are released.

So, in summary, this report highlights the new treatment guidelines for uncomplicated gonococcal infection from the CDC. To recap: The recommendation is a single dose of intramuscular ceftriaxone at 500 mg. And this is supported by both pharmacokinetic as well as pharmacodynamic data. If chlamydia infection has not been ruled out, adding doxycycline 100 mg twice a day for seven days is advised. We've been able to implement this change in our clinic. I encourage you to read the full article as it might help with your patient care as well as your clinical practice.

[07.08] Paper #2

Bachmann LH, Kirkcaldy RD, Geisler WM, Wiesenfeld HC, Manhart LE, Taylor SN, Seña AC, McNeil CJ, Newman L, Myler N, Fuchs R, Bowden KE; MAGNUM Laboratory Working Group. Prevalence of *Mycoplasma genitalium*infection, antimicrobial resistance mutations, and symptom resolution following treatment of urethritis. Clin Infect Dis. 2020 Dec 17;71(10):e624-e632. **[PubMed Abstract]**

The next article to discuss is titled "Prevalence of *Mycoplasma genitalium* infection, antimicrobial resistance mutations, and symptom resolution following treatment of urethritis," and this was written by Dr. Bachmann and colleagues and published in *Clinical Infectious Diseases* in November of 2020. This article was referenced in the same *MMWR* we just discussed about the treatment of gonorrhea. And it was an example of the impact that dual antibiotic exposure for gonococcal infection might potentially increase the resistance for other

bacterial STIs.

1. In this study, men with urethritis symptoms were enrolled for about one year in six different sexual health clinics in the U.S., and urethral specimens were tested for *Mycoplasma genitalium* (or Mgen for short). Mgen-positive specimens were evaluated for various resistance-associated mutations, and that was either to the macrolides, such as azithromycin, or fluoroquinolone antibiotics.

2. They evaluated 914 men with urethritis and found that 29% had evidence of Mgen—so pretty high percentage. The prevalence was similar to that of chlamydia and gonorrhea in this population.

3. Among those patients with Mgen and available resistance results, 64% were found to have macrolide resistance-associated mutations and 12% had mutations associated with fluoroquinolone resistance. Now, of note, genotypic mutations don't always lead to actual clinical treatment failure, but it is concerning.

4. There were 670 men without *Trichomonas vaginalis* who had azithromycin included in their regimen as part of their initial urethritis treatment and completed a follow-up survey. Twenty-six percent with Mgen with macrolide resistance mutations reported persistent symptoms on their follow-up survey. What's interesting, but I can't fully explain, is that 17% of men without Mgen also had persistent symptoms. It's possible they just had another reason or etiology for their urethritis.

In summary, this article looked at the prevalence of Mgen at different sites in the U.S. and found that greater than 25% of men with urethritis had Mgen. Macrolide resistance-associated mutations were very common—over 60%. Now, one might think this might be due to frequent or recent exposure to azithromycin in antibiotic treatment regimens. But, for this study, the authors did not find a clear association between resistance and antibiotic exposure in the prior 14 days.

[09.41] Paper #3

Gernert KM, Seby S, Schmerer MW, Thomas JC 4th, Pham CD, Cyr SS, Schlanger K, Weinstock H, Shafer WM, Raphael BH, Kersh EN; Antimicrobial-Resistant *Neisseria gonorrhoeae* Working Group. Azithromycin susceptibility of *Neisseria gonorrhoeae* in the USA in 2017: A genomic analysis of surveillance data. Lancet Microbe. 2020 Aug;1(4):e154-e164. **[PubMed Abstract]**

Another article that was referenced in the *MMWR* was one published by Dr. Gernert and colleagues titled "Azithromycin susceptibility of *Neisseria gonorrhoeae* in the USA in 2017: A genomic analysis of surveillance data." This was published in *The Lancet Microbe* in August 2020.

1. This study looked at the genomic analysis of *Neisseria gonorrhoeae* isolates from the U.S. Gonococcal Isolate Surveillance Project, and it evaluated the strain types associated with decreased susceptibility to azithromycin.

2. The authors sorted 410 isolates into different clades. And, they found a predominant clade with 63% of its isolates with a decreased susceptibility to azithromycin, and this was indicated by a minimum inhibitory concentration (or MIC) value that was equal to or greater than 2 µg/mL. With the rest of the 313 isolates, 18% had decreased susceptibility to azithromycin with MIC values actually at greater than or equal to 4 µg/mL.

3. The reduced susceptibility to azithromycin is focused on two main resistance mechanisms: There's a 23S rRNA variant, as well as a mosaic multiple transferable resistance (or MTR) operon, and it encodes an efflux pump. For the resistance mechanisms, I'm not sure how much this is relevant clinically for the individual patient, but it has implications for public health. For example, it is important if antibiotic-resistance variant strains predominate or transfer resistance to susceptible isolates. *Neisseria gonorrhoeae* is fascinating in the way it acquires resistance to antibiotics, and I encourage you to read up more on this if you have time.

4. Worldwide, there are increasing reports of gonococcal isolates with decreased azithromycin susceptibility. This has also been shown in the U.S. through the Gonococcal Isolate Surveillance Project. And this article highlights the prevalence of isolates for which azithromycin just may no longer be effective as treatment.

[11.41] Summary
To conclude, I'd like to summarize some key points from this session:

1. There are new treatment recommendations from the CDC for uncomplicated gonococcal infection and this involves a higher single dose of intramuscular ceftriaxone at 500 mg.

2. Antimicrobial stewardship is one reason to support these recommendations, and the prevalence of macrolide resistance-associated mutations is high among men with *Mycoplasma genitalium* urethritis.

3. The percentage of *Neisseria gonorrhoeae* isolates with reduced susceptibility to azithromycin is increasing in the U.S.

Thank you for listening. Have a wonderful day.

[12.20] Credits
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