Hot Topic

National STD Curriculum Podcast

How to Treat Gonorrhea Without Ceftriaxone

May 19, 2023

Season 3, Episode 13

This episode reviews three articles about four antimicrobial treatment options for Neisseria gonorrhoeae other than ceftriaxone.

Topics:

- Gonorrhea
- antimicrobial
- ertapenem
- STI

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Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
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Transcript

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introduction**[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.

background**[00:20] Background**
If you work in a clinic that sees a high number of patients with *Neisseria gonorrhoeae*, treatment of this bacteria is at the forefront of one's mind. Ceftriaxone, which is given as a single 500 mg intramuscular dose, is the first choice antibiotic for the empiric treatment of gonorrhea in the U.S. as well as many other countries, but there are rare circumstances when ceftriaxone just may not be an option. A situation might occur if a patient has a severe allergy to the third-generation cephalosporins (for example, anaphylaxis). Or the detection of a *Neisseria gonorrhoeae* strain with resistance to both ceftriaxone and azithromycin, which was reported in both the United Kingdom and Australia. So what can you do? With no new drugs currently available that effectively treat *Neisseria gonorrhoeae*, recycling older drugs or drugs that are rarely used routinely for this STI [sexually transmitted infection] are now being explored. Now, antimicrobial stewardship is really important, and so one always has to weigh the risks and benefits of different antibiotics when trying to treat an infection, and so this is a concept we're going to touch on in this episode.

paper-1**[01:28] Paper #1**

de Vries HJC, de Laat M, Jongen VW, et al. Efficacy of ertapenem, gentamicin, fosfomycin, and ceftriaxone for the treatment of anogenital gonorrhoea (NABOGO): a randomised, non-inferiority trial. Lancet Infect Dis. 2022 May;22(5):706-717. **[PubMed Abstract]**

This first article for review was published in *Lancet Infectious Diseases* in May of 2022 by Dr. de Vries and colleagues. It is titled "Efficacy of ertapenem, gentamicin, fosfomycin, and ceftriaxone for the treatment of anogenital gonorrhea: A randomized, non-inferiority trial." I'm going to focus a bit more time on this article.

1. Now, this was a double-blind, randomized, controlled trial to assess whether ertapenem, gentamicin, or fosfomycin monotherapy are efficacious alternatives to ceftriaxone monotherapy for the treatment of uncomplicated anogenital gonorrhea. They had three experimental arms and one control arm, and they did this study at the Centre for Sexual Health in Amsterdam, the Netherlands, and the study was conducted from 2017 to 2020. Participants had to have a positive anorectal or urogenital NAAT [nucleic acid amplification test] for *Neisseria gonorrhoeae* and then they were randomly assigned to one of four treatment groups.
2. In these groups, participants received either a single dose of intramuscular ceftriaxone 500 mg, intramuscular ertapenem 1,000 mg, intramuscular gentamycin at 5 mg/kg, or oral fosfomycin at six grams in one dose. Now, whatever treatment the participant received, they also received placebo to replace the other antimicrobial agents, so they were blinded to treatment allocation. They didn't know which treatment they were getting. The primary outcome was successful treatment of the primary anatomical site of infection in each group by a NAAT-negative test-of-cure.
3. They enrolled 346 participants, and most of the participants (or 90%) were MSM (or men who have sex with men); 21% were living with HIV.
4. What the authors found is that in the primary protocol analysis, clearance of the infection occurred in 100% of participants in the ceftriaxone group, 99% in the ertapenem group, 93% in the gentamycin group, and only 12% in the fosfomycin group. They then analyzed clearance of *Neisseria gonorrhoeae* per site of infection, and what they found is that both ceftriaxone and ertapenem cleared 100% of the urethral infections. But for pharyngeal infections, 90% were cleared with ceftriaxone, 88% with ertapenem, and only 26% with gentamicin.
5. They also did a modified intention-to-treat analysis, and in that setting, the participants without a test-of-cure were considered as a treatment failure. But in this specific analysis, ertapenem did not meet the non-inferiority criterion to ceftriaxone or gentamycin.
6. Diarrhea was reported more often with ertapenem and fosfomycin compared with ceftriaxone.

Overall, this randomized study showed that a single dose of intramuscular ertapenem 1000 mg was non-inferior to a single dose of intramuscular ceftriaxone 500 mg for the treatment of uncomplicated anogenital gonorrhea. The non-inferiority of ertapenem to ceftriaxone was not established in the modified intention-to-treat analysis, but this was really an unlikely assumption that all six participants without a test-of-cure failed

treatment. I do find this interesting that gentamicin didn't seem to work as well in clearing *Neisseria gonorrhoeae* anogenital infection. And I was also concerned that pharyngeal infections had lower rates of clearance with all the antibiotics used, although ceftriaxone was the best.

I really enjoyed reading this manuscript because it helps explore other possible treatments for *Neisseria gonorrhoeae*that haven't been used before. Now fosfomycin is a desirable option, but it was found to be ineffective in this study, which is unfortunate because it would be nice to have more oral options to treat this organism. In terms of using ertapenem, I don't see us using this medication on a routine basis for *Neisseria gonorrhoeae* treatment. And so this gets back to the idea of antimicrobial stewardship. Antibiotics, in general, are important to treat infections, but we also need to protect patients from potential harm caused by unnecessary antibiotic use. We also need to be concerned about minimizing antibiotic resistance in bacterial pathogens, both for the individual person as well as in the community. Ertapenem is a more broad-spectrum antibiotic, and it's often used in the infectious disease world for multidrug-resistant organisms, which we can't use other antibiotics. For example, there's just not other options available, and so this paper was helpful because, in that rare circumstance where you don't have the option of using ceftriaxone, ertapenem might be a possible antimicrobial agent that you can use. But again, I see this in a very rare occurrence. The authors do point out that it's unclear whether ertapenem will be effective for gonococcal infections after, let's say, unsuccessful treatment with ceftriaxone— for example, in the setting of resistance to ceftriaxone. And this is because both antibiotics might have the same resistance pathways, and, really, further study is needed in this area.

paper-2**[06:23] Paper #2**

Barbee LA, Soge OO, Morgan J, et al. Gentamicin alone is inadequate to eradicate *Neisseria gonorrhoeae* from the pharynx. Clin Infect Dis. 2020 Nov 5;71(8):1877-1882. **[PubMed Abstract]**

The findings from this [previous] study leads us to review the second article, which was published in *Clinical Infectious Diseases* by Dr. Barbee and colleagues. This article is titled "Gentamicin alone is inadequate to eradicate *Neisseria gonorrhoeae* from the pharynx," and it was published in November of 2020.

1. Between 2018 and 2019, MSM with a NAAT-positive pharyngeal gonorrhea were enrolled in a single-arm, unblinded clinical trial to evaluate gentamycin for the treatment of pharyngeal gonorrhea. And the plan was to enroll 60 participants.
2. Men received a single intramuscular dose of gentamicin 360 mg and underwent a test-of-cure by culture 4 to 7 days later. The authors elected to use a higher dose of gentamycin, and this was based on established pharmacokinetic/pharmacodynamic data, as gentamicin exhibits concentration-dependent bactericidal activity.
3. During this time period, they enrolled 13 participants with pharyngeal gonorrhea, but due to the poor efficacy of gentamycin to treat their infections the study was stopped early. Of the 13 enrolled participants, only two were cured at the pharynx.
4. Efficacy was not associated with gentamicin peak concentration or the minimum inhibitory concentration.

This study showed that gentamicin alone as monotherapy, even at the elevated dose of 360 mg— and that's higher than what's recommended by the CDC for uncomplicated infection—was insufficient to eradicate *Neisseria gonorrhoeae*from the pharynx. This study is unique because it was one of the first to evaluate gentamicin efficacy at this body site and in the absence of a second microbial agent. Previous studies provided gentamycin with azithromycin and suggest that the efficacy of gentamicin observed in those other trials might actually reflect the efficacy of the two grams of azithromycin that was given in those studies that may have been active against some susceptible isolates.

paper-3**[08:24] Paper #3**

Li X, Le W, Lou X, et al. In vitro activity of ertapenem against *Neisseria gonorrhoeae* clinical isolates with decreased susceptibility or resistance to extended-spectrum cephalosporins in Nanjing, China (2013 to 2019). Antimicrob Agents Chemother. 2022 May 17;66(5):e0010922. **[PubMed Abstract]**

Unemo M, Golparian D, Limnios A, et al. In vitro activity of ertapenem versus ceftriaxone against *Neisseria gonorrhoeae* isolates with highly diverse ceftriaxone MIC values and effects of ceftriaxone resistance determinants: Ertapenem for treatment of gonorrhea? Antimicrob Agents Chemother. 2012 Jul;56(7):3603-9. **[PubMed Abstract]**

The question that came up in the study by Dr. de Vries is whether ertapenem can treat *Neisseria gonorrhoeae* that is resistant to ceftriaxone. Now, we don't have much data on this topic, but an article was published in *Antimicrobial Agents and Chemotherapy*, and it touched on this point. It was published in May 2022 by Dr. Li and colleagues and is titled "In vitro activity of ertapenem against *Neisseria gonorrhoeae* clinical isolates with decreased susceptibility or resistance to extended-spectrum cephalosporins in Nanjing, China (2013 to 2019)."

1. During this time period, 259 strains of *Neisseria gonorrhoeae* were included, and these strains were isolated from men with symptomatic urethritis who had attended an STD clinic at the Institute of Dermatology in Nanjing, China. And they demonstrated, these isolates demonstrated, decreased susceptibility or resistance to ceftriaxone and cefixime as defined by the World Health Organization.
2. Now, let's take a step back because I'd like to define some terms that were mentioned in this study. The MIC stands for minimum inhibitory concentration, and what it is, is the lowest concentration of an antibiotic at which bacterial growth is inhibited in vitro. Now, MIC 50 represents the antibiotic concentration at which 50% or more of isolates are inhibited, and the MIC 90 is the concentration that would inhibit 90% of isolates.
3. The criteria used for the decreased susceptibility to ceftriaxone was an MIC of 0.125 mg/L or greater, and for cefixime, it was an MIC of 0.25 mg/L or greater.
4. The authors found that the MIC 50 of ertapenem was 0.032 mg/L and substantially lower than that of observed for ceftriaxone and cefixime. The MIC 90 for ertapenem was 0.125 mg/L, and it was similar to the MIC 90 observed for ceftriaxone but lower than that MIC 90 for cefixime. They did find nine isolates, or 3.5%, that was fully resistant to ceftriaxone and cefixime, but what was encouraging is that based on the MIC values, ertapenem would be effective against these nine isolates. Overall, 83% and 96% of *Neisseria gonorrhoeae* isolates had ertapenem MICs below the ceftriaxone and cefixime susceptibility breakpoints, respectively.
5. They found that the penA mosaic allele, which is known to be present in many *Neisseria gonorrhoeae* strains that possess decreased susceptibility to the extended-spectrum cephalosporins, including ceftriaxone, was present at a significantly higher proportion of isolates with higher ertapenem MICs. They also found that ertapenem susceptibilities of isolates containing the penA mosaic allele were lower than the susceptibilities of isolates that lacked the mosaic allele.

In summary, this study found that ertapenem might be effective to treat *Neisseria gonorrhoeae* isolates with decreased susceptibility or resistance to ceftriaxone or cefixime. I've only provided a brief summary here, so I encourage you to take a look at this article if you're interested in learning more about this topic. Also, another article that was published in the same journal by Dr. Unemo and colleagues in 2012 covers similar points, and it talks about the in vitro activity of ertapenem versus ceftriaxone against *Neisseria gonorrhoeae* isolates with diverse ceftriaxone MIC values.

summary**[11:52] Summary**

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

1. Intramuscular ertapenem is non-inferior to intramuscular ceftriaxone for the treatment of uncomplicated anogenital gonorrhea infection. But antimicrobial stewardship considerations should be

taken into account when considering this antibiotic for use;
2. Gentamicin monotherapy is not effective to treat *Neisseria gonorrhoeae* in the pharynx; *and*
3. In vitro data suggests ertapenem may be effective in treating *Neisseria gonorrhoeae* isolates that are resistant to ceftriaxone and cefixime.

credits**[12:26] Credits**

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