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Literature Review

National STD Curriculum Podcast

Syphilis: A 2024 Update

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Season 5, Episode 2

This episode discusses five recent articles on syphilis including the effectiveness of linezolid and azithromycin, a new penicillin allergy testing algorithm, and a successful integrated response to address a syphilis epidemic in a rural American Indian community.

Topics:

- Syphilis
- STD
- STI
- penicillin
- azithromycin
- antimicrobial

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Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
Consulting Fee: Innoviva Specialty Therapeutics

References

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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**[00:21] Background**

A few articles have been recently published on syphilis, and it would be great to share in this episode. Some have to do with antimicrobial therapy against *T. pallidum*, which is pertinent considering the most recent benzathine penicillin G shortage, and some have to do with strategies to deal with the syphilis epidemic. So, here are a few summaries of articles I thought were interesting to review in this episode.

paper-1**[00:46] Paper #1**

Close RM, Weigle A, Thompson T, McAuley J. Integrated response to address a resurgent syphilis epidemic in a rural American Indian community, Whiteriver, Arizona, January 2022 to June 2023. Sex Transm Dis. 2024 Mar 1;51(3):156-161. **[PubMed Abstract]**

The first article we're going to cover was published in *Sexually Transmitted Infections,* and it was published in March 2024 by Dr. Close and colleagues. It's titled "Integrated response to address a resurgent syphilis epidemic in a rural American Indian community, Whiteriver, Arizona, January 2022 to June 2023." I'm going to spend a bit more time on this manuscript.

The rates of syphilis have greatly increased in American Indian and Alaska Native populations, and the reasons for this are many but include under-resourced health care systems in these communities. An American Indian community in Northeastern Arizona was found to have an increase in syphilis cases from 2017 through 2021. And the increase in cases in this community outpaced increases in syphilis that were seen both statewide as well as nationally.

1. The Whiteriver Service Unit is an acute care hospital and it provides public health services as well as medical care to this community. The Whiteriver Service Unit implemented strategies to address this increase in syphilis cases, which they talk about in this manuscript. These strategies included partner engagement, enhanced screening practices, health record modifications, as well as increased syphilis testing capacity. These strategies were implemented in June 2022 and the authors analyzed syphilis cases prior to and after these measures were put in place.
2. Now, Table 1 in this manuscript has a nice list of the policy and practice changes they implemented. I'm not going to go through all the details, but here are a few to mention. The Whiteriver Service Unit initiated and maintained regular meetings with Tribal Division of Health and Emergency Operations Center. They advised local hospitals to update STI screening and treatment policies and then also facilitated partnership between the Inter Tribal Council of Arizona and local Tribal health for media campaign and testing support in the community.
3. In addition to those strategies, they also implemented an opt-out STI screening for all patients presenting for a pregnancy test, weekly chart reviews of all reactive syphilis tests, and for every patient with a reactive syphilis test, implemented a syphilis health summary that included prior syphilis testing and treatment, staging, as well as a next plan of action in the EHR (or electronic health record). And, I can imagine that was really helpful for providers who are seeing these patients in the moment to know their syphilis history. New standing orders for nurses and pharmacists were initiated to expand screening, diagnosis, and treatment, and they acquired point-of-care test kits for syphilis testing by fingerstick.
4. The authors found that from January 2022 to June 2023, there were 277 new cases of syphilis; 55% of these new cases were among women and 16% of these cases were among women who were pregnant. Around 60% of the new infections during this time frame were staged as late latent or of unknown duration. There were three congenital infections and all of these occurred between January and June of 2022. And just a reminder, the new strategies were implemented in June 2022.

5. What the authors found is that when the new strategies were implemented, there was a *decrease* in the median time to treatment initiation from a peak of six days in the early 2022 period to a nadir of one day in the later months of 2022.
6. Syphilis infections also declined by 65% after program implementation. There was a peak of 20 infections per month that decreased to seven infections per month by June of 2023 after the strategies were implemented. And there were no cases of congenital syphilis after program implementation through the analysis period.

In this community, the Whiteriver Service Unit serves as the primary health care center as well as a public health service on tribal land of northeastern Arizona. And by implementing measures to improve the EHR, provider and community engagement, as well as increase syphilis testing, this group observed a greater than 50% increase in testing, greater than 80% reduction in time-to-treatment initiation, and greater than 60% reduction in new infections with *no*further new cases of new congenital syphilis. This is a big deal, and I encourage you to read this manuscript if you'd like to learn more about their program strategies which might be relevant to your clinic, practice, or community.

paper-2**[05:26] Paper #2**

Ubals M, Nadal-Baron P, Arando M, et al. Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: A prospective, open-label, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2024 Apr;24(4):404-416. **[PubMed Abstract]**

The next article to discuss was published in *Lancet Infectious Diseases* in April of 2024 by Dr. Ubals and colleagues. This article is titled "Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB study) in Spain: A prospective, open-label, non-inferiority, randomized controlled trial."

1. So, this was an open-label, randomized, controlled trial, and it was conducted at multiple sites in Spain, and it assessed the efficacy of linezolid 600 mg once daily for 5 days to treat early syphilis, and they compared it with a single intramuscular injection of benzathine penicillin G 2.4 million units. Fifty-nine patients were either assigned to getting linezolid or benzathine penicillin G.
2. The authors chose a once-a-day regimen for linezolid to simplify the regimen as well as potentially improve adherence and, based on pharmacokinetic-pharmacodynamic calculations, they expected this dosage to be effective.
3. They used a composite endpoint that included clinical response, serological response, as well as absence to relapse to document cure of syphilis. They also used molecular sequencing in cases of recurrent symptoms to syphilis to help determine antibiotic failure versus reinfection.
4. What they found is that 70% of the participants in the linezolid group and 100% of participants in the benzathine penicillin G group responded to treatment for early syphilis. The study was stopped after the interim analysis for futility.

I really think it would be nice to have a variety of antimicrobial therapy options to treat syphilis, especially in the setting of severe drug allergies or drug shortages. Linezolid is an antibiotic that has shown activity against *T. pallidum* in vitro and in rabbit models. However, what the authors found in this study is that linezolid at 600 mg once daily for 5 days was not effective to treat early syphilis compared to a single intramuscular injection of benzathine penicillin G 2.4 million units. Now, typically, for bacterial infections, we use linezolid 600 mg twice a day, so it is possible that once-a-day dosing of linezolid was just not frequent enough or that a longer duration of treatment was needed in order to achieve cure.

paper-3**[07:50] Paper #3**

Lieberman NAP, Reid TB, Cannon CA, et al. Near-universal resistance to macrolides of *Treponema pallidum* in North America. N Engl J Med. 2024 Jun 13;390(22):2127-2128. **[PubMed Abstract]**

Briefly, I'd also like to review a letter that was published in *The New England Journal of Medicine* in June of 2024 by Dr. Lieberman and colleagues. It is titled "Near-universal resistance to macrolides of *Treponema pallidum* in North America."

This group found that 99% of 604 *T. pallidum* strains that were sampled in North America from 2017 through 2023 were genotypically resistant to azithromycin. Samples were collected from patients in 13 U.S. states, Washington D.C., as well as two Canadian provinces. And what these data show is that a provider should really not use azithromycin as a treatment option for syphilis, and it reflects the increasing prevalence of macrolide resistance among *T. pallidum* strains.

paper-4**[08:42] Paper #4**

Lillis RA, Barbee LA, McNeil CJ, et al. Randomized multicenter trial for the validation of an easy-to-administer algorithm to define penicillin allergy status in sexually transmitted infection clinic outpatients. Clin Infect Dis. 2024 May 15;78(5):1131-1139. **[PubMed Abstract]**

The next article to review was published in *Clinical Infectious Diseases* in May of 2024 by Dr. Lillis and colleagues. It is titled "Randomized multicenter trial for the validation of an easy-to-administer algorithm to define penicillin allergy status in sexually transmitted infection clinic outpatients."

1. In this setting, the authors used either penicillin skin testing or a graded oral challenge to evaluate penicillin allergy in individuals at low risk for penicillin allergy. The authors determined a low-risk penicillin allergy group based on a questionnaire that was developed to stratify risk.
2. Two hundred eighty-four (284) participants enrolled in the study, and there were 72 participants who were excluded from further allergy evaluation for various reasons, including 67 who were found to have a high-risk reaction to penicillin.
3. Therefore, 212 participants were determined to be low-risk, and of these, 206 participants completed the allergy assessment as the final per-protocol population. The 206 low-risk participants were eligible for penicillin allergy evaluation and then randomized to either receive penicillin skin testing or the graded oral challenge of penicillin.
4. One-hundred-two (102) participants underwent penicillin skin testing, and 96 of these participants (or 94%) were identified as not allergic to penicillin; 104 participants completed the graded oral challenge, and 95 of these participants (or 91%) were determined to not have a penicillin allergy.
5. The group found that all immediate reactions were mild and responded to antihistamines. One participant had a delayed reaction that required a course of steroids.

The authors note that around 15% of patients in STI clinics report penicillin allergies, which can make it challenging to treat some STIs, for example, like syphilis. And this report found that over 90% of participants determined low risk did not have a penicillin allergy and were able to have the allergy actually removed from their medical record. The algorithm is available in this article if you're interested in learning more, and it can be useful in STI clinic settings, especially where access to an allergy and immunology specialist is limited.

paper-5**[11:11] Paper #5**

Dionne JA, Giacani L, Tamhane A, et al. Prevalence and predictors of oral *Treponema pallidum* detection by quantitative polymerase chain reaction in early syphilis. J Infect Dis. 2024 Jun 14;229(6):1628-1636. **[PubMed Abstract]**

An article was published in *Journal of Infectious Diseases* in June of 2024 by Dr. Dionne and colleagues. It is titled "Prevalence and predictors of oral *Treponema pallidum* detection by quantitative polymerase chain reaction in early syphilis."

1. At this time, there are no commercially available FDA-approved molecular diagnostic tests for syphilis in the U.S.
2. And this was a small study evaluating *T. pallidum* DNA in 32 men with early syphilis, and they used quantitative PCR, targeting a portion of tp0574, and it's a highly conserved *T. pallidum* gene.
3. Around 19% of participants had primary syphilis, 56% had secondary syphilis, and 25% had early latent syphilis. Syphilis was staged by experienced providers with physical examination, as well as a standard serological testing with positive treponemal and nontreponemal antibody detection and titers.
4. They found that 44% of the study participants had oral *T. pallidum* shedding that was detected by quantitative PCR, and they found that oral detection was more common in persons with secondary and early latent syphilis.
5. In the absence of oral lesions, oral quantitative PCR detection was 38%, so pretty high. The median organism burden at the oral site was highest during secondary syphilis, which makes sense because, usually, those patients have a high treponemal bacterial load.

This study suggests that molecular testing of syphilis at the oral site can be helpful in the diagnosis of syphilis, even in the absence of lesions. They found that the highest proportion of men with oral shedding occurred in those with secondary as well as early latent syphilis.

summary**[12:53] Summary**

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

1. Strategies around partner engagement, enhanced screening practices, health record modifications, and increased testing capacity can reduce new syphilis infections in American Indian communities.
2. Linezolid 600 mg daily for 5 days is not an effective treatment for early syphilis.
3. Ninety-nine percent of *T. pallidum* strains sampled in North America were genotypically resistant to azithromycin.
4. It's possible for low-risk patients to undergo either penicillin skin testing or a graded oral challenge in an outpatient STI clinic to evaluate for penicillin allergy.
5. Oral shedding of syphilis based on molecular detection can occur in the absence of lesions, and quantitative PCR positivity was highest in those with secondary and early latent syphilis.

credits**[13:50] Credits**

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