Hot Topic

National STD Curriculum Podcast

New Recommendations for Complicated Syphilis

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Season 2, Episode 2

This episode reviews key updates on the diagnosis and treatment of complicated syphilis in the 2021 STI Treatment Guidelines.

Topics:

- Syphilis
- ocular syphilis
- otosyphilis
- neurosyphilis

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Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
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Transcript

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[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.

[00.23] Background
This episode will focus on the new 2021 STI Treatment Guidelines that were recently released by the CDC [Centers for Disease Control and Prevention] in July. I'm going to talk about some key updates on complicated syphilis presented in the new guidelines. But it will be a brief review, so I encourage you to take a look at the full report, which is easily accessed online. There are also webinars available through the National Network of STD Clinical Prevention Trainings Centers (NNPTC), as well as updates on the National STD Curriculum if you want to learn more.

[00.56] Topic #1 Syphilis: Changes in workup and management

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(No. RR-4):1-187.
[2021 STI Treatment Guidelines]

Let's start out discussing the changes in the workup and management of neuro[syphilis], oto[syphilis], and ocular syphilis. Syphilis that goes to the brain, the eye, or the ear can occur at any stage of syphilis, so patients *do* need to be asked if they have symptoms regardless of their stage of disease. Now, there is a common misconception that neurosyphilis only occurs during tertiary disease, and that's simply just not true. So, if someone presents with syphilis, even primary or latent disease, ask about vision, hearing, or neurologic changes. With regards to the workup for oto and ocular syphilis, in the 2021 STI Treatment Guidelines, there is a decreased emphasis on the need for lumbar puncture. Now, if patients have clinical evidence of neurologic involvement—let's say they have cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or signs of meningitis or stroke—and these all can occur when patients might also present with oto or ocular syphilis, then a lumbar puncture with CSF [cerebral spinal fluid] examination should be performed and ideally before starting treatment.

[01.58] Topic #2 Ocular syphilis: Diagnosis and treatment

Dunaway SB, Maxwell CL, Tantalo LC, Sahi SK, Marra CM. Neurosyphilis treatment outcomes after intravenous penicillin G versus intramuscular procaine penicillin plus oral probenecid. Clin Infect Dis. 2020 Jul 11;71(2):267-273. **[PubMed Abstract]**

But let's say a patient comes in with a new diagnosis of syphilis and they have isolated ocular symptoms. They should have a full ocular examination, and if evidence of ocular abnormalities, but no evidence of cranial nerve dysfunction, then a CSF examination is not necessary before treatment. So you don't need to do the lumbar puncture. Now, what if the patient has ocular symptoms but an ocular examination is normal? Then the guidelines suggest a CSF analysis might be helpful to look for neurosyphilis. The ophthalmologists we work with have been fantastic about getting these patients in quickly for an ocular exam. But sometimes, for whatever reason, there might be a delay in the patient's visit with ophthalmology. In this situation, when you can't get a quick confirmation of a diagnosis of ocular syphilis, you can perform a lumbar puncture to evaluate the CSF. If the CSF results are concerning for neurosyphilis, these results might help me to start the appropriate treatment sooner. I recognize many providers don't have immediate access to lumbar punctures or an ophthalmology evaluation for their patients, or their patients might just refuse a lumbar puncture, and that's happened in our clinic before. So, I think you really have to do the best that you can with the resources available to you. Now, with regards to treatment, similar to the past recommendations, those patients with a diagnosis of ocular syphilis should be treated just as if they have neurosyphilis—so that would be IV penicillin G for 10-14 days.

Now, IV penicillin can be difficult to administer. For example, patients might need to be admitted to the hospital, or outpatient parenteral antimicrobial therapy (also known as OPAT), usually through an Infectious

Disease Clinic, needs to be in place to get the recommended treatment. As an alternative, one can use daily injections of procaine penicillin intramuscularly with oral probenecid for 10-14 days. Now, our clinic has had good experience with using procaine penicillin for neuro, oto, and ocular syphilis, and we've had success with this treatment, which can be given on an outpatient basis. There was an article published by Dr. Dunaway and colleagues in *Clinical Infectious Diseases* in July of 2020. It was titled "Neurosyphilis treatment outcomes after intravenous penicillin G versus intramuscular procaine penicillin plus oral probenecid." The study showed that neurosyphilis outcomes—and that was specifically looking at CSF white blood cell counts and CSF VDRL [venereal disease research laboratory] reactivity normalization—were not different for IV versus procaine penicillin. So, in a lot of cases of neuro, oto, and ocular syphilis, procaine penicillin might be adequate treatment if patients are willing and able to come in daily, can take oral probenecid during this time, and there is clinical staff available to administer on weekends and holidays. I will mention, though, that if a patient presented with actual vision loss as opposed to spots or floaters, most clinicians would favor IV penicillin for therapy.

[04:51] Topic #3 Otosyphilis: Diagnosis and treatment

Marra CM, Maxwell CL, Ramchandani M, Tantalo LC, Sahi SK, Dunaway SB, Litvack JR. Hearing loss in individuals at risk for neurosyphilis. Int J STD AIDS. 2020 Oct;31(12):1178-1185. **[PubMed Abstract]**

Now for otosyphilis, the 2021 STI Treatment guidelines recommend that if patients have isolated auditory symptoms and a normal neurologic exam, lumbar puncture with CSF examination is no longer recommended before treatment. The reason for this is that the results of the CSF are likely to be normal in these settings, and the results would not alter the treatment. It probably relates to the pathogenesis of how syphilis affects the ear. The patient should also be seen by otolaryngology and then treated with the same regimen as used for neurosyphilis. If you're interested in learning more about otosyphilis, Dr. Marra and colleagues published an article in the *International Journal of STD and AIDS* in October of 2020. They found almost 50% of those patients with syphilis had hearing loss using a portable audiometer. Hearing loss was not related to syphilis stage, but older age and CSF pleocytosis increased the likelihood of otosyphilis in this study.

[05.50] Topic #4 Syphilis treatment and normalization of rapid plasma reagin (RPR) titer

Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis. 2008 Oct 1;47(7):893-9.
[PubMed Abstract]

Xiao Y, Tong ML, Lin LR, Liu LL, Gao K, Chen MJ, Zhang HL, Zheng WH, Li SL, Lin HL, Lin ZF, Yang TC, Niu JJ. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. Sci Rep. 2017 Aug 30;7(1):9911. **[PubMed Abstract]**

The STI guidelines mention that the normalization of serum RPR [rapid plasma reagin] titer predicts the normalization of abnormal CSF parameters after neurosyphilis treatment. Therefore, repeat CSF examinations are unnecessary for persons without HIV or persons with HIV who are on antiretroviral therapy. The guidelines don't indicate the time frame for the normalization of the RPR titers in the serum, so I personally might use the timeframe for the stage of syphilis that person presented with. For example, for early disease, within 12 months. The guidelines reference an article published by Dr. Christina Marra in *Clinical Infectious Diseases* in 2008, in which they found the normalization of serum RPR titer—and that was defined as a 4-fold decrease in titer or reversion of the test to nonreactive—correctly predicts the success of treatment of neurosyphilis in most cases and follow up lumbar punctures are just not necessary. The authors found that 57% of patients had normalized serum RPR titer by four months after treatment and 88% of patients by 13 months. The normalization of serum RPR titer predicted the normalization of other CSF and clinical abnormalities in over

80% of patients at four months and over 90% of patients at 13 months. The second article referenced in the guidelines was published by Dr. Xiao and colleagues in *Scientific Reports* in 2017. This article was titled "Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients." In this article, up to 91% of patients showing serological response of RPR in the serum also achieved normalization of the CSF leukocyte count.

Overall, this might make it much easier for follow-up of clinical care if patients have serological and clinical improvement after treatment. Now, one question that has come up, if a patient has neuro, oto, or ocular syphilis and was adequately treated, when would I do a follow-up RPR? Now, my practice has been in about three months, and that's just to make sure the RPR is not increasing, which would really suggest reinfection or possible failure of treatment. In terms of the time frame for when an appropriate serologic response to treatment should occur, I would follow the 2021 STI Treatment Guidelines for the stage of syphilis disease. For example, those with primary or secondary disease, a 4-fold decline in titers usually occurs by 12 months after treatment.

[08:24] Summary
To conclude, I'd like to summarize some key points from this session:

1. Patients with ocular syphilis who do not have signs or symptoms of neurosyphilis do not need a lumbar puncture for CSF examination before treatment.
2. Patients with otosyphilis who have isolated auditory symptoms and a normal neurological examination do not need a lumbar puncture for CSF examination before treatment, as the CSF results are likely to be normal in these settings.
3. Normalization (or a 4-fold decline) of the serum RPR titer after treatment for neuro, oto, or ocular syphilis should be sufficient to predict the success of treatment for this disease. Therefore, a repeat lumbar puncture is not necessary in those persons without HIV or persons with HIV on antiretroviral therapy.

Thank you for listening, and have a wonderful day.

[09.16] Credits
This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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