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Hot Topic

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Neurosyphilis Treatment Options

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This episode reviews recent literature published on treatments for neurosyphilis other than IV penicillin.

Topics:

- STI
- STD
- Syphilis
- neurosyphilis

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Disclosures

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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.

[00.20] Background
With rising rates of syphilis in the U.S. as well as other high-income nations, we're subsequently seeing more complicated manifestations of this disease, such as neurologic, otic, and ocular syphilis. The CDC 2021 STI

Treatment Guidelines recommend patients with neurologic, otic, or ocular syphilis receive intravenous aqueous crystalline penicillin G—and for brevity, I'm going to say IV penicillin—or as an alternative regimen, intramuscular procaine penicillin G—and likewise for brevity, I'm going to say IM procaine penicillin—plus oral probenecid for a total of 10-14 days. Now, if penicillin can't be used, the guidelines indicate that intramuscular or intravenous ceftriaxone daily for 10-14 days is an option for treating neurosyphilis, although the data to support this regimen is very limited. For patients I see with neurologic, otic, or ocular syphilis, I treat with either IV penicillin or IM procaine penicillin plus oral probenecid except in the rare isolated case in which a patient can't or won't get one of these two treatment options, for whatever reason. Sometimes, the recommended treatment is just not feasible for a particular case. There have been a few articles recently published on this topic that I'd like to review in this episode.

[01.40] Paper #1

Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: A retrospective multicentre study. Lancet Infect Dis. 2021 Oct;21(10):1441-1447. doi: 10.1016/S1473-3099(20)30857-4. Epub 2021 May 26. Erratum in: Lancet Infect Dis. 2021 Aug 5. **[PubMed Abstract]**

The first article to review was published by Dr. Bettuzzi and colleagues in *Lancet Infectious Diseases* in October of 2021. It is titled "Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: A retrospective multicenter study."

1. This was a retrospective cohort study including patients with neurosyphilis treated at one of eight tertiary care centers in France from January 1997 through December of 2017.
2. The diagnosis of neurosyphilis was made when a patient presented with positive syphilis serology, otic, ocular, or neurologic symptoms, and CSF [cerebrospinal fluid] results that indicated neurosyphilis. In this particular study, CSF results indicating a diagnosis of neurosyphilis included one of the following: either a positive CSF VDRL [venereal disease research laboratory] or CSF *T. pallidum* PCR [polymerase chain reaction] test or more than five leukocytes on CSF cell count.
3. Now, patients received either IV ceftriaxone 2 grams once daily or IV penicillin at 3-4 million units every 4 hours for at least 10 days. They included a total of 208 patients with neurosyphilis. For treatment, 42 of those patients received ceftriaxone, and 166 patients received penicillin.
4. Now, it's important to note that the two groups differed in terms of the clinical type of neurosyphilis patients were diagnosed with at the beginning. For example, uveitis was more frequent in the IV penicillin treatment group: So 54% had uveitis in the IV penicillin treatment group compared to 33% in the ceftriaxone group. And a higher proportion of patients in the penicillin group had a positive CSF-VDRL result. So in the IV penicillin group, there were 48% of patients with a positive CSF-VDRL result compared to 28% in the ceftriaxone group. So, the two groups differing in terms of clinical type of neurosyphilis might have influenced the type of treatment given and potentially the response to therapy. For example, if patients had more severe disease, they were given IV penicillin.
5. The authors looked at how many patients had an overall clinical response, and that included either a complete or partial clinical response at one month after treatment. They found 41 patients, or 98%, in the ceftriaxone treatment group had an overall clinical response compared to 125 patients, or 76%, in the IV penicillin group. After propensity score weighting, and this was used to try to help reduce the indication bias of treatment allocation, the overall clinical response rates remained different between the groups. There was no significant difference in the number of patients with a complete response, and that was a total disappearance of neurologic or ocular symptoms in either treatment group after propensity score weighting.
6. Serological response, which was defined as a 4-fold decline in serum VDRL titer, to treatment at six months did not differ between the groups. There was an 88% response in the ceftriaxone group versus an 82% response in the IV penicillin group.

So, this was a very well written article that showed, at least in this particular study, ceftriaxone was at least

as effective as IV penicillin for the treatment of neurosyphilis. I do want to point out that this was not a randomized trial, and it is possible that the patients in the ceftriaxone group had less severe symptoms at baseline. The authors appropriately mention that the number of patients in each subgroup was small, and while these results support the use of ceftriaxone as an alternative to IV penicillin for the treatment of neurosyphilis, there's a need for randomized, controlled trials to help confirm these results. So what I take from this article is that it adds to the body of literature helping to support other treatments for neurosyphilis when one can't give the recommended (or alternative) treatment regimen for a particular patient case.

[05.33] Paper #2

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. Erratum in: Clin Infect Dis. 2021 Mar 1;72(5):911. **[PubMed Abstract]**

In our clinic, we have a lot of experience using IM procaine penicillin with oral probenecid for the treatment of patients with neurologic, otic, or ocular syphilis, especially in those who have more mild symptoms. This treatment is attractive because it can be given on an outpatient basis without the use of a PICC [peripherally inserted central catheter] line. I find this treatment option is patient preferred, and the majority of patients show up for their daily injections. So, what has been published recently on the use of IM procaine penicillin for neurosyphilis? This was an article published in *Clinical Infectious Diseases* in July of 2020 by Dr. Dunaway and colleagues. It is titled "Neurosyphilis treatment outcomes after intravenous penicillin G versus intramuscular procaine penicillin plus oral probenecid."

1. Participants were enrolled in a study of CSF abnormalities in syphilis conducted at the University of Washington from 2003 to 2014. Participants had clinical or serological evidence of syphilis and neurological symptoms such as symptomatic meningitis, vision or hearing loss, or stroke. *Or* the patients were asymptomatic but had risk factors that were associated with increased risk for neurosyphilis.
2. Study participants were treated with IV penicillin or the combination of IM procaine penicillin plus oral probenecid. The authors then analyzed 150 participants found to have CSF abnormalities consistent with neurosyphilis and were treated with one of these two regimens. There were 32 participants who were treated with IV penicillin and 118 participants who were treated with IM procaine penicillin plus oral probenecid. The median serum RPR [rapid plasma reagin] titer was 1:128, and the majority of participants, or 77%, had HIV. The CD4 and HIV viral load data was available for 103 individuals. For those persons with HIV, the median CD4 count was 392, and 23 patients, or 22%, had HIV RNA levels that were <50 copies/mL.
3. CSF white blood cell counts and CSF-VDRL reactivity normalized in almost all individuals by 12 months after treatment. There was no significant relationship found between the different treatment regimens for neurosyphilis and CSF normalization of any measure. On multivariate analysis, CSF-VDRL reactivity was more likely to normalize in participants with symptomatic neurosyphilis and less likely to normalize in those with late-stage syphilis. Late-stage syphilis includes those with late-latent syphilis as well as syphilis of unknown duration.
4. The authors found that serum RPR was more likely to normalize in those with higher pretreatment titer and less likely to normalize in late syphilis. Among those participants with HIV, CSF white blood cell counts and CSF-VDRL reactivity were more likely to normalize in those treated with ARVs [antiretrovirals], possibly suggesting CSF pleocytosis might have been in part due to HIV and not necessarily neurosyphilis.

My key takeaway from this study is that treatment outcomes for neurosyphilis, defined by normalization of CSF, was not different for those participants receiving IV penicillin or IM procaine penicillin with probenecid, regardless of HIV status.

[08.49] Paper #3

Girometti N, Junejo MH, Nugent D, McOwan A, Whitlock G; 56 Dean Street Collaborative Group. Clinical and serological outcomes in patients treated with oral doxycycline for early neurosyphilis. J Antimicrob Chemother. 2021 Jun 18;76(7):1916-1919. **[PubMed Abstract]**

The third article to discuss was published in March of 2021 in the *Journal of Antimicrobial Chemotherapy* by Dr. Girometti and colleagues. It is titled “Clinical and serological outcomes in patients treated with oral doxycycline for early neurosyphilis.”

1. The authors in this study analyzed outcomes for patients diagnosed with early neurosyphilis and treated either with IM procaine penicillin with oral probenecid or high-dose oral doxycycline at 56 Dean Street. 56 Dean Street is a great model of a sexual health and HIV service clinic that’s based in London. If you’re not familiar with 56 Dean Street and Dean Street Express, I encourage you to take a look at their website.
2. The authors defined early neurosyphilis as patients with acute onset of neurologic, otic, or ocular symptoms and a new syphilis diagnosis based on a positive syphilis serological test in the last year.
3. The authors mention that a lumbar puncture for CSF evaluation was offered to patients according to presenting symptoms and clinical judgment and performed in 52 patients overall, so about 60%. There were seven patients in the doxycycline treatment group who had a lumbar puncture performed, and these results were available in a supplementary table. I need to digress for a moment to talk about the availability of CSF results, as it’s not clear whether these patients had evidence of neurosyphilis based on the CSF studies. All seven patients who had a lumbar puncture in the doxycycline treatment group had CSF white blood cell counts less than 5. There were five patients with a positive CSF TPPA [*Treponema pallidum* particle agglutination assay], but the TPPA titer was not routinely performed, and six out of the seven patients had a negative CSF-VDRL or RPR.
4. So now, let’s take it back to the study. They included 87 patients; 53% were persons with HIV, and 40% had a previous diagnosis of syphilis in the past; 62 patients, or 71%, received a combination of IM procaine penicillin plus oral probenecid for 14 days, and 16 patients, or 18%, received oral doxycycline 200 mg twice a day for 28 days. Two of the patients receiving doxycycline were lost to follow-up, so they had follow-up on 14 patients in the doxycycline group. The rest of the patients were treated with another type of therapy.
5. The median RPR titer for the patients receiving IM procaine penicillin was 1:128 and for those treated with doxycycline was 1:64.
6. The authors report serological response in all patients who received treatment with either regimen, and 91% of patients reporting full symptom resolution at 30 days post-treatment.

So while I think this information is helpful, the authors correctly point out that we need more studies to establish the effectiveness of doxycycline in the treatment of neurosyphilis. It’s encouraging that so many patients did well with doxycycline, although it is possible that some of the patients did not actually have neurologic, ocular, or otic syphilis. Although these results need to be interpreted with caution, I’m glad the authors reported their findings. There have been those rare isolated cases where I can’t just use one of those first-line recommended treatments for whatever reason—that’s when I might consider oral doxycycline. But, I’m going to prioritize treating patients with IM procaine penicillin with probenecid or IV penicillin because there’s just a lot more data to support these two therapies, and those are what are recommended in the guidelines. I look forward to hearing more on this topic in the future.

[12.23] Summary

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

1. The CDC 2021 STI Treatment Guidelines recommend patients with neurologic, otic, or ocular syphilis receive IV penicillin or, as an alternative regimen, IM procaine penicillin plus oral probenecid for a total

of 10-14 days.
2. There are increasing data to support daily ceftriaxone for neurosyphilis treatment, but a randomized, controlled trial is really needed to better address this issue.
3. Normalization of CSF in patients with neurosyphilis was *not* different for those receiving IV penicillin or IM procaine penicillin with probenecid.
4. And our clinical experience has been that IM procaine penicillin with probenecid is a useful alternative treatment regimen for neurosyphilis that can be administered on an outpatient basis.
5. We need more studies to establish the effectiveness of doxycycline in the treatment of neurosyphilis.

[13.19] Credits

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