Ocular Syphilis or Neurosyphilis?
The November EyeNet Clinical Update “Be on the Lookout for Ocular Syphilis”1 and the recent CDC “Clinical Advisory: Ocular Syphilis in the United States”2 mentioned in the article raise questions regarding the optimal management of syphilitic eye disease. Both documents equate all types of ocular syphilis with neurosyphilis. Accordingly, the Clinical Advisory states, “A lumbar puncture with cerebrospinal fluid (CSF) examination should be performed in patients with syphilis and ocular complaints. Ocular syphilis should be managed according to treatment regimens for neurosyphilis.”

The Clinical Advisory defines an “ocular syphilis case” as “a person with clinical symptoms or signs consistent with ocular disease (i.e., uveitis, panuveitis, diminished visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis) with syphilis of any stage.”

Presumably, additional causes of decreased visual acuity would be considered before peremptorily attributing low vision or blindness to syphilis. Most ophthalmologists would reasonably agree that uveitis, vitritis, retinitis, retinal vasculitis, and optic neuritis in a person with reactive serologic confirmation of syphilis signal neurosyphilis and should be managed with a penicillin treatment regimen recommended for neurosyphilis. Some would also advise CSF evaluation to uncover asymptomatic neurosyphilis in a seropositive patient with scleritis.

What is the justification that interstitial keratitis and other forms of stromal keratitis are necessarily neurosyphilis? Similarly, what about other ophthalmic manifestations of syphilis outlined in the comprehensive table of acquired and congenital syphilis in the online version3 of the EyeNet article, such as granulomatous conjunctivitis, dacyroadenitis, and orbital periostitis?

We propose that neurosyphilis is no more likely in patients with syphilitic stromal keratitis than among people with untreated latent syphilis.4 Indications for lumbar puncture in a patient with syphilitic keratitis would include optic atrophy, neuroretinitis, posterior uveitis, sclerouveitis, pupillary abnorality, cranial nerve palsy, HIV infection, or a high nontreponemal test titer.4 Contrary to the proposal to treat all patients with any form of ocular syphilis with a neurosyphilis treatment regimen, an alternative approach is to use the treatment regimen for late latent syphilis for a previously untreated patient who has syphilitic keratitis but who does not have scleral or posterior segment inflammation or neurological abnormality.4

We and other corneal and external disease specialists consider adult-onset syphilitic stromal keratitis, with or without mild iritis, to be either a late manifestation of congenital syphilis or late syphilis of unknown duration, not neurosyphilis. For this entity, we would care for a previously untreated patient using the recommended regimen for late latent syphilis, namely, intramuscular benzathine penicillin G, 3 doses of 2.4 million units each given at 1-week intervals,5 and would not routinely advise a lumbar puncture in the absence of other clinical signs.

The recommendation that patients with any form of ocular syphilis incur the potential risks of a lumbar puncture and the costs of a regimen involving intravenous aqueous crystalline penicillin G or intramuscular procaine penicillin with probenecid for 10 to 14 days requires further supportive evidence and risk-benefit analysis.

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A Response From the CDC
The letter by Drs. Jones and Wilhelmus entitled “Ocular Syphilis or Neurosyphilis?” highlights the nuances related to the diagnosis of syphilis, including ocular syphilis, which are important given the current syphilis epidemic in the United States. Syphilis cases increased between 2012 and 2013, and in 2014 there was a 15% increase compared with 2013.1 After clusters of ocular syphilis cases were reported2 and a Clinical Advisory issued,3 CDC began collecting reports of cases. To date, over 150 cases of ocular syphilis have been reported to CDC from 2014 and 2015. Most cases (over 90%) are in men, especially in men who have sex with men (MSM). Several of the cases have resulted in significant sequelae, including blindness. In some cases, there was a delay in final

3 www.aao.org/eyenet/article/be-on-lookout-ocular-syphilis.
diagnosis and treatment due to the lack of awareness of ocular syphilis.

Given the number of cases reported, CDC has worked with both local and national partners to increase awareness of ocular syphilis as a cause of eye inflammation, which can occur in any stage of syphilis. We also encourage syphilis diagnostic testing with treponemal and nontreponemal testing in any patient with visual complaints without another known cause among those at risk, especially MSM and those who are HIV infected.

While ocular syphilis can have a variety of clinical manifestations, the most common presentation of ocular syphilis is uveitis, which is consistent with cases reported to CDC. Interstitial keratitis is a relatively rare presentation of ocular syphilis, accounting for only 1% of cases diagnosed with keratitis in a British national surveillance of ocular syphilis.4 Of note, none of the 2014-2015 cases reported to CDC have presented with interstitial keratitis. In addition, a high proportion of these patients with ocular manifestations have a high RPR titer and/or a positive cerebrospinal (CSF) Venereal Disease Research Laboratory (VDRL) test. Of cases reported to the CDC currently, 96% of cases have a rapid plasma reagin titer ≥1:16, and of cases with a lumbar puncture and CSF VDRL, 70% were positive.

The 2015 STD Treatment Guidelines state that “Syphilitic uveitis or other ocular manifestations (e.g., neuroretinitis and optic neuritis) can be associated with neurosyphilis. A CSF examination should be performed in all instances of ocular syphilis, even in the absence of clinical neurologic findings. Ocular syphilis should be managed in collaboration with an ophthalmologist and according to the treatment and other recommendations for neurosyphilis, even if a CSF examination is normal.”5 Recommended treatment for neurosyphilis and ocular syphilis is IV aqueous penicillin G for 10-14 days. In addition, while CSF examination is recommended, this should not delay treatment. Coordination with an infectious disease specialist can be beneficial to get appropriate diagnostic testing, treatment, and long-term follow-up.

Thank you again for your continued effort to increase awareness of ocular syphilis.

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