Syphilis continues to be a burden on the public health system. While men who have sex with men and HIV-infected individuals are the most affected populations, syphilis rates have also increased in reproductive-aged women, resulting in concurrent increases in congenital syphilis. Prompt diagnosis and treatment are requisite components of syphilis control.

Syphilis, an old disease caused by the spirochete Treponema pallidum, continues to create a huge burden for our public health system and is a major cause of morbidity. In the 20th century, syphilis peaked in the 1940s, followed by a rapid decline with the widespread availability and use of penicillin. However, despite The New York Times article suggesting that the “end of syphilis seen by the use of penicillin” was probable [1], rates did not dramatically plummet until decades later, through the implementation of an aggressive syphilis eradication program. Despite the intercurrent increase of syphilis cases paralleling the AIDS epidemic, the United States experienced an all-time low of syphilis cases in the year 2000. Unfortunately, these gains in controlling the syphilis epidemic have not been sustained [2].

Nationally, we have seen high rates of syphilis concurrent with new HIV infections, most prominently in the community of men who have sex with men (MSM). Paralleling this, increased rates of syphilis have been observed in women of reproductive age, resulting in increased rates of congenital syphilis infections [3]. The Southern United States, historically a setting with a higher proportion of socially and economically disadvantaged communities compared with other areas of the country, has been severely impacted by this syphilis epidemic. For example, North Carolina experienced a 40% increase in the number of cases of syphilis over the last year, higher than we have seen in the past decade (Figure 1).

Nationally, extreme racial and ethnic disparities exist, with African American men and women representing the majority of cases [4]. Similarly, syphilis rates in North Carolina are highest among black/African American males (Figures 2–4) and among those less than 30 years of age (Figure 5). Further, MSM and HIV-infected individuals comprised nearly 50% of the new early syphilis infections in 2014 [5]. Similar to the country as a whole, North Carolina has seen an increase in rates of syphilis in reproductive-aged women and, consequently, increased numbers of cases of congenital syphilis. Presently, the highest numbers of syphilis cases occur in North Carolina’s most populous counties including Mecklenburg, Wake, Guilford, Durham, and Cumberland.

An important component of syphilis control involves screening individuals at the highest risk for infection and those in whom there is a high potential for complications. Thus, current screening guidelines support syphilis serologic screening for all MSM and HIV-infected individuals. The frequency of screening is determined based on risk, although screening should be performed at least annually in this group, with follow-up screening every 3–6 months for individuals with ongoing high-risk behaviors. This includes individuals reporting multiple or anonymous sexual partners, those engaging in sexual intercourse without the use of barrier protection, and individuals having sex while under the influence of illicit drugs. Routine screening is also recommended for all pregnant women at the first prenatal visit, with follow-up screening in the third trimester and at the time of delivery in at-risk individuals [6].

Early syphilis, specifically primary and secondary syphilis, remains easiest to diagnose based on characteristic physical exam findings. The diagnosis of syphilis can be confirmed with widely available serologic screening tests, keeping in mind that no single test is sufficient to make the laboratory diagnosis of syphilis. In addition, up to 30% of early primary chancre may be associated with a nonreactive rapid plasma reagin (RPR) test, and therefore it remains important for the provider to initiate therapy for individuals with lesions suspicious for early syphilis at the time of their initial presentation, instead of waiting for serologic confirmation.

The traditional syphilis serologic screening algorithm involves a blood draw for a nontreponemal test such as RPR...
or venereal disease research laboratory (VDRL). Reactive initial screens are typically confirmed with a treponemal antigen test such as treponemal palladium particle agglutination, florescent antibody-absorption, chemiluminescence immunoassay (CIA), or enzyme immunoassay (EIA). In a move towards high-volume automated testing, some laboratories are now performing “reverse sequence screening,” in which they start with EIA or CIA as the initial screen, followed by a nontreponemal test if the initial test is reactive. This reverse screening strategy may result in considerably more false-positive results in settings or populations where there is a low baseline prevalence of syphilis [7].

Diagnosis of advanced stages of syphilis may present some challenges. This was recently highlighted by a clinical advisory regarding ocular syphilis from the Centers for Disease Control and Prevention [8]. Ocular syphilis, a neurosyphilis equivalent, presents with decreased visual acuity and involvement of almost any eye structure, although posterior uveitis or panuveitis remains the most common manifestation. The consequences of ocular syphilis may be devastating, with the potential for progression to permanent visual impairment and blindness. Initial cases were reported on the West Coast in 2014, predominantly in HIV-infected men. Ultimately, cases were reported across the country, including in North Carolina; to date, over 200 cases have been reported in the United States [8, 9]. Thus, in cases of suspected or confirmed ocular syphilis, prompt neurologic examination; referral for ocular evaluation; syphilis serologic testing; and lumbar puncture with cerebrospinal fluid (CSF) evaluation of cell count, protein, and CSF VDRL should occur.

It should be noted that there have been reports of nontreponemal serologic tests showing nonreactive results despite overt findings of syphilis, particularly in patients with early syphilis. More common in early syphilis, this “prozone phenomenon” occurs when there is a high antibody titer that can interfere with the antigen-antibody lattice for-
Information, resulting in a false-negative result on a nontreponemal screening test (ie, RPR or VDRL). Acknowledging this dilemma, it may be useful to notify the clinical lab regarding this concern, especially in situations where early syphilis is suspected. Given the current epidemiology of syphilis infection, vigilance in detecting the subtle signs of syphilis and promoting more testing, screening, and timely treatment to avoid transmission and untoward complications of this disease is certainly warranted.

Optimal treatment of syphilis has remained unchanged for over 6 decades. Penicillin remains the treatment of choice for all stages of the disease. To prevent transmission and potential complications of untreated disease, treatment should be initiated immediately if the constellation of syphilis findings is present, instead of waiting for serologic confirmation of disease. Early syphilis is typically treated with one injection of benzathine penicillin G 2.4 million units in a single intramuscular dose. Late latent syphilis, syphilis of unknown duration, or tertiary syphilis is treated with benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly, each at 1-week intervals. Pregnant women should also be treated with the penicillin regimen that coincides with their stage of infection. Because penicillin is the only acceptable regimen for syphilis in pregnancy, women with a true allergy to penicillin should be referred for desensitization. Neurosyphilis and ocular syphilis require a 14-day course of aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours or as a continuous infusion. Additionally, at the conclusion of the
intravenous regimen, some experts recommend benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each, at 1-week intervals, to encompass treatment for advanced or tertiary disease [6].

Finally, it is of the utmost importance to maintain an open line of communication with local health departments when a clinical and/or laboratory diagnosis of syphilis is made in order to ensure adequate and timely notification and treatment of the patient’s sexual partner. Given the high HIV/syphilis coinfection rate and the literature supporting syphilis as a risk factor for HIV acquisition, care should include counseling regarding high-risk behavior and should provide avenues for comprehensive HIV and sexually transmitted disease screening and prevention.

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