Syphilis
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Hello, I am Doctor Victoria Mobley and I am a medical epidemiologist for the Communicable Disease Branch in North Carolina. This presentation will cover the natural history of syphilis infections, as well as current diagnosis and treatment recommendations.

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The goals of this presentation are to review the organism that causes syphilis, Treponema pallidum; describe key differences in the clinical presentation of primary and secondary syphilis; review the commonly used testing algorithms for syphilis; review the CDC approved treatment regimens; identify where disease information can be accessed including the case definitions for the different syphilis stages; and finally to where guidance on how to report syphilis infections to North Carolina's statewide Electronic Disease Surveillance System can be found

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Syphilis has been around for thousands of years. It is caused by a motile spirochete bacterium, meaning it looks like a corkscrew, called Treponema pallidum. This organism enters the body at the site of inoculation thru a breach in the squamous or columnar epithelial cells after which it spreads via the host's lymphatic system. Syphilis is spread by vaginal, anal or oral intercourse and pregnant women can transmit this infection to their unborn children.

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The time from exposure to symptom onset is approximately 3 weeks, but can range anywhere from 10 to 90 days. The first clinical presentation of infection is the development of a sore or multiple sores, called chancres, which are shallow painless ulcers at the site where the organism enters the body. Because chancres are painless and can present in hard to visualize areas of the body, like the mouth or rectum as depicted in these pictures, they often go undetected. Chancres are self-limited, and will heal between 3 and 12 weeks after developing regardless of treatment.

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Secondary syphilis develops between 4 and 10 weeks after the appearance of the primary lesion, usually presenting as a small, macular rash that can be mistaken for many different conditions or illness (such as viral or tick-borne infections). Additionally, when present on individuals with darker skin, the rash can be missed altogether. Syphilitic rashes may also involve the palms of the hand and soles of the feet, which may be easier to spot on individuals

with darker skin. Therefore a careful and thorough skin examination should be performed on all clients presenting to STD clinics or any individual with risk factors for a STI. Other potential symptoms of secondary syphilis include patchy alopecia –depicted in the top right photo, which occurs in approximately 5% of secondary syphilis cases. Condylomata lata, as shown in the bottom photo, are flat, gray-white-appearing lesions that may be mistaken for genital warts and are teeming with spirochetes and thus are highly infectious lesions. This manifestation of secondary syphilis occurs in approximately 10-20% of cases. Similar to the primary chancre, condylomata lata lesions will resolve regardless of treatment.

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This slide lays out the course of untreated syphilis infection over the course of 10-30 years. Of 100 individuals who develop primary syphilis, all will go on to develop secondary syphilis. A quarter of individuals with untreated syphilis will recover, possibly due to being treated for some other incidental infection, such as strep throat or community acquired pneumonia. Three-quarters of the individuals with secondary syphilis will progress to latent syphilis, of which 30 will experience recurrent secondary syphilis. After a decade or more, approximately 30 of the 100 infected individuals with untreated syphilis cases will progress to tertiary syphilis which can present with cardiovascular and central nervous system disease. From a public health standpoint, our concern is that first year of infection because that is when syphilitic lesions, which are necessary for transmission of infection (except perinatally), are present.

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Symptoms of syphilis may present before the body has the chance to develop antibodies that can be detected through testing. A still commonly used method of diagnosing early syphilis is through the direct visualization of organisms using a darkfield microscope, which when positive gives a definitive diagnosis of syphilis. When available this diagnostic method can provide rapid results. The disadvantages of darkfield microscopy include the need for specialized equipment and staff trained in this procedure. Also specimens must be processed rapidly, and even when that occurs false negatives are still possible. Lastly, it is unclear how well darkfield microscopy performs on oral lesions.

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There are two categories of blood tests for syphilis: the non-treponemal and treponemal tests. The non-treponemal tests which include the RPR and VDRL, measures antibodies directed against a cardiolipin-lecithin-cholesterol antigen which is not specific for Treponema pallidum. The non-treponemal tests are both quantitative and qualitative and the titer usually correlates with disease activity. It is important to note that RPR and VDRL are not interchangeable, meaning if you diagnosis someone with a RPR titer of 1:128, that does not correlate to a VDRL titer of 1:128, therefore when monitoring for an appropriate response to treatment the same diagnostic test should be used. The advantages of the non-treponemal tests are that they are rapid and cheap, can often be performed during the clients clinic visit, can be used to evaluate

response to therapy-by following decreases in titers- and can be used to assess for possible reinfection. The disadvantages are that the sensitivity of these tests vary by stage of disease and certain medical conditions can result in false positive results (such as rheumatoid disorders, IV drug use, chronic infections, HIV infection, or advanced age). Non-treponemal tests usually revert to negative following treatment.

The treponemal tests which include enzyme immunoassays (EIA), treponema pallidum particle agglutination (TPPA) and fluorescent treponemal antibody (FTA-ABS), measures antibodies directed against T. pallidum antigens. These tests are qualitative and once positive usually remain reactive for life. Until recently – meaning the last several years- the treponemal specific tests have been used to confirm a positive non-treponemal test.

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The sensitivity of the various syphilis tests are shown in this table. As you can see, the sensitivity of the treponemal specific tests is higher than that of non-treponemal specific tests during the primary syphilis stage, especially the EIA test. By the secondary syphilis stage, both the non-treponemal and treponemal specific tests perform equally well.

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So let's now talk about how syphilis is typically diagnosed. On the left is what is referred to as the "traditional" syphilis screening algorithm, which uses a non-treponemal test for the initial screen. If it is negative, then no further testing is done unless the clinical presentation is concerning for a false negative result. If the non-treponemal test is positive, a treponemal specific test such as TP-PA or FTA-ABS is used to confirm the diagnosis. The major advantage of the traditional algorithm is that it detects active infection. The disadvantages are related to the high rate of biologic false positive non-treponemal test results, which make confirmation with a treponemal test necessary. Also the traditional algorithm can miss early primary and treated infection.

The algorithm on the right is increasingly being used to diagnosis syphilis and is generally referred to as the "reverse" screening algorithm. This algorithm uses a treponemal specific test such as the EIA, as the initial screening test. If this is negative, no further testing is done unless clinically indicated. Positive EIAs are followed by a quantitative non-treponemal tests (i.e. the RPR or VDRL test), which if positive, confirms the syphilis diagnosis. If the results of the treponemal and non-treponemal specific tests are discordant then a second treponemal test is used to determine whether infection is present or not. The advantage to using this reverse screening algorithm instead of the traditional one is that it is relatively cheap because it is automated allowing for a high throughput (which makes it low cost in high volume settings). The disadvantage is that we cannot distinguish between active disease and old disease and there is still significant confusion regarding the appropriate management of patients with discrepant serologies (EIA+ and RPR negative).

Something that all clinicians should consider is that regardless of the various testing results, if syphilis is clinically suspected or the patient had a recent sexual partner with known syphilis, empiric treatment for syphilis should occur.

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In North Carolina, the Disease Intervention Specialists follow up on all primary, secondary and early latent syphilis cases to identify their sexual contacts and make sure they get evaluated and treated for syphilis. The CDC recommended treatment for primary, secondary and early latent syphilis is benzathine penicillin G 2.4 million units IM for a single does. Treatment failures, late latent syphilis or syphilis of unknown duration is treated with benzathine penicillin G 2.4 million units IM once weekly for 3 weeks. Alternative regimens for the treatment of non-neurosyphilis in PCN allergic patients consists of two weeks of doxycycline or tetracycline – though doxycycline is preferred over tetracycline due to easier dosing. I would like to take just a moment to emphasize that pregnant women should never be treated with an alternative regimen. If a pregnant woman is diagnosed with syphilis and has a documented allergy to penicillin she will need to be desensitized and then treated with PCN. This usually requires the woman be referred to a physician or even hospitalized to arrange for the desensitization but treatment with PCN is critical to preventing syphilis infection in her unborn child.

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Treatment response is typically determined by following the RPR or VDRL titers. An appropriate RPR/VDRL titer change following appropriate treatment is a 4-fold drop so for example a RPR titer of 1:256 that drops to 1:64 following treatment, would be indicate an appropriate treatment response. Follow-up periods for checking the RPR/VDRL titers varies depending on HIV status: for HIV-negative individuals, RPR/VDRL titers should be checked at 6, 12 and 24 months. For HIV-positive individuals, there may be a slower RPR/VDRL titer decrease so titers should be checked at 3, 6, 9, 12 and 24 months.

Individuals deemed high-risk for repeat syphilis infection should be retested every 3-6 months.

Additionally, due to shared modes of transmission, HIV and syphilis infections are often diagnosed in the same populations. The presence of syphilitic lesions increases the likelihood of acquiring HIV by 2 to 5 fold. This is why every individual diagnosed with syphilis should also be tested for HIV, unless already known to be positive.

Sexual contacts of early syphilis cases should receive epi treatment, based on timing of exposure and syphilis stage of index case. For example, for primary syphilis index cases, any sexual contacts within 3 months should receive empiric treatment.

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Detailed information on syphilis can be found on the North Carolina Public Health website – highlighted in blue here, including links to the CDC website where the case definitions for the different syphilis stages are located.

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A link to the disease reporting forms can also be found on the North Carolina Public Health website. Additionally, there is an Epidemiologist on call 24/7 who can assist you with questions on investigation or reporting of communicable diseases, and the number can be found on the same website. That concludes this syphilis presentation and I hope you found it informative. Thank you.