Syphilis

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Syphilis is a chronic bacterial infection caused by *Treponema pallidum* that is endemic in low-income countries and and occurs at lower rates in middle-income and high-income countries. The disease is of both individual and public health importance and, in addition to its direct morbidity, increases risk of HIV infection and can cause lifelong morbidity in children born to infected mothers. Without treatment the disease can progress over years through a series of clinical stages and lead to irreversible neurological or cardiovascular complications. Although syphilis is an ancient disease and the principles of recommended management have been established for decades, diagnosis and management are often challenging because of its varied manifestations and difficulty in interpretation of serological tests used to confirm diagnosis and evaluate response to therapy. In North America and western Europe, incidence of syphilis has increased dramatically in the past decade among men who have sex with men, particularly those with coexistent HIV infection. Only one drug, penicillin, is recommended for syphilis treatment and response to therapy is assessed based on changes over months in serological test titres. Treatment for patients who cannot receive penicillin and management of patients who do not serologically respond to treatment are common clinical problems.

Introduction

Syphilis is a chronic bacterial infection caused by *Treponema pallidum*, subspecies *pallidum*. The disease has been recognised by clinicians and the general public for hundreds of years. Over the same period, the disease has been highly stigmatised, which has hampered intervention strategies such as screening and partner notification.[1] In low-income and middle-income countries (LMICs), syphilis infection is a relatively common problem that is a source of substantial morbidity, including adverse pregnancy outcomes and acceleration of HIV transmission.[2] By contrast, in western Europe and the Americas, disease rates have tended to fluctuate periodically, challenging both clinicians and public health practitioners during highs then declining after strengthened control efforts, only to re-emerge after a period of lower disease incidence.[3–5] Syphilis incidence has again begun to increase dramatically in western Europe and the Americas, and now disproportionately occurs among men who have sex with men (MSM).[3–5]

Clinical manifestations, transmissibility to others, and recommended treatment vary over the natural history of infection.[6] Although readily recognisable in name to both clinicians and the general public, control efforts have sometimes been hampered by poor familiarity with syphilis clinical manifestations, diagnosis, and management. In this Seminar I will review the current epidemiology of syphilis and diagnosis and management strategies for general clinicians; a group who are now increasingly likely to see patients with current or past infection.

Search strategy and selection criteria

I searched PubMed to identify peer-reviewed articles published in English between Jan 1, 2005, and June 30, 2016, using the terms "syphilis", "syphilis epidemiology", and "syphilis treatment". I also referred to older literature on management and clinical presentations of the disease written in the pre-penicillin era.

Epidemiology

Worldwide more than 5 million new cases of syphilis are diagnosed every year, with most infections occurring in LMICs where infections are endemic and congenital infections are not uncommon.[2,3] Led by WHO, antenatal screening programmes have reduced maternal and infant syphilis by more than one third, and congenital syphilis has been eliminated in at least one nation (Cuba).[3] By contrast, in higher-income countries, infection is less common and occurs disproportionately in people living on the margins of society such as those in poverty, people with poor access to health care, or those in racial, ethnic, and sexuality minority populations.[4,5] In high-income countries, syphilis is transmitted largely within tight sexual and social networks, a characteristic that contributes to the observation that although the disease is relatively uncommon, more than 15–20% of people in the USA diagnosed with syphilis every year have been infected before.[7–9] By contrast with the epidemic seen in the USA during the 1990s largely in heterosexual people in association with a concomitant epidemic of crack cocaine use, the current resurgence in western Europe and the Americas has disproportionately affected MSM and has been closely linked with HIV infection.[4,5] This pattern of periodic resurgence of syphilis occurs within a 10–15 year time period and has variously been attributed to either failure to sustain control efforts, changing risk behaviours (such as crack cocaine use), and waxing and waning partial host immunity to infection at the population level.[10]

Since soon after the recognition of the HIV epidemic, epidemiologically, syphilis has been closely associated with HIV infection.[11,12] Syphilitic genital ulcers are densely infiltrated with lymphocytes (the primary target cells for HIV infection) and so provide a portal of entry for HIV acquisition, as well as a focus for HIV (as well as syphilis) transmission to others.[13] In 2014 in the USA,

about 40% of all people diagnosed with early syphilis were infected with HIV at the time of syphilis diagnosis and, in some locations,[4] 3·5–4% of those who were HIV-negative at the time of infection became infected with HIV in the year after diagnosis. HIV incidence has been reported to be up to 20% in the decade after syphilis diagnosis.[14,15] Additionally, investigators have suggested that in people with HIV, the clinical manifestations of syphilis or the response to recommended therapy could be different as a result of the effect of HIV on host immunity. However, when carefully studied, differences have most often not been statistically significant, reaffirming the substantial variability in clinical manifestations of the disease.[16,17] Additionally, patients receiving treatment for HIV might be more closely studied and more regularly followed-up after syphilis diagnosis, which might introduce an ascertainment bias favouring variability in syphilis presentation and response to therapy among people with HIV confection.

Although syphilis is a chronic infectious disease that might cause morbidity throughout its natural history, the infection is transmissible to others (with the exception of congenital infection) for only the first few years of infection, which has led public health control efforts to focus on the primary, secondary, and early latent stages of infection, sometimes referred to as infectious syphilis. After 2–3 years of untreated infection, sexual transmission is rare and the major consideration shifts to personal morbidity including late neurosyphilis and cardiovascular and gummatous infections.

Pathogenesis

Syphilis is caused by *Treponema pallidum*, subspecies *pallidum*, a long thin (from 0·15 µm by 6 µm to 15 µm), slowly growing bacterium that cannot be cultured for clinical purposes. *T pallidum*, subsp *pallidum* is closely related (>99% DNA homology) to other pathogenic spirochaetes including *T pallidum* subsp *pertenue*, the causative agent of yaws, and *Treponema carateum*, the organism that causes pinta.[18] The high degree of DNA homology between subspecies has permitted use of syphilis serological tests for the diagnosis of non-syphilitic treponemal diseases such as yaws. In areas where both infections are found, this can lead to confusion as to which infection a patient with a reactive serological test has.

With the exception of congenital syphilis, syphilis is spread mainly through direct lesion contact, although a small proportion of infections are spread through blood transfer (eg, during direct blood transfusions or needle sharing during injection drug use). Because of the organism's slow growth, infection has a long incubation period, taking about 3 weeks from the time of inoculation to the appearance of initial (primary) lesions at the site of inoculation.[6,19] Unlike for other sexually transmitted infections, this long incubation period between disease acquisition and development of infectious lesions provides the opportunity to interrupt syphilis transmission.[19] Without intervention, the organism then disseminates widely through the bloodstream and to the CNS where it might subsequently produce varying clinical manifestations of infection.[6]

Clinical presentations and natural history

The natural history of syphilis is one of a chronic infection that can cause a series of highly variable clinical manifestations during the first 2–3 years of infection, followed by a typically prolonged latent stage that can evolve into clinically apparent tertiary infection stage years or even decades after initial infection.[6,20] Because syphilis lesions are often asymptomatic and can occur in regions of the body where they might go unnoticed, not all infected people have classic signs of one or more of the clinical stages of infection. The disease is sexually infectious to others only when the early, primary and secondary stages are present; however, congenital transmission can occur years after entering latency.

Primary syphilis refers to when a primary or initial lesion is present at the site of inoculation of infection. In primary syphilis the main clinical manifestation is the presence of a painless, usually solitary, indurated, clean-based ulcerative lesion that typically appears about 2–3 weeks after direct contact with another person's infectious lesion. Although chancres are most often seen in men on the distal penis, they can be located at nearly any place where direct contact with another infected person's lesion might occur and although sometimes unnoticed, are well described in the female vagina and cervix, in and near the rectum, and in the mouth, as well as on other potentially exposed body parts such as fingers, the neck. Genital ulcers mimicking chancres are most commonly caused by genital herpes but can be caused by chancroid, trauma, fixed drug eruptions, and other dermatological processes (table 1).[21] The primary chancre can be accompanied by tender or non-tender regional lymphadenopathy. *T pallidum* is present and might be demonstrable in specimens from the lesion base. Without treatment, after a period of 3–6 weeks, primary lesions spontaneously resolve without scarring. With treatment, lesions begin to resolve within a few days.

Secondary syphilis is the most commonly recognised clinical syndrome of syphilis, particularly among women or MSM, presumably because painless internal vaginal or anogenital lesions of primary syphilis have been overlooked. After, or sometimes coexistent, with the primary lesion, secondary manifestations of infection result from haematogenous dissemination of infection. Although the classic manifestation of secondary syphilis is a painless, macular rash of 1–2 cm, reddish or copper coloured, lesions on the palms of the hands or soles of the feet, the rash of secondary syphilis is extraordinarily variable in appearance, can be discrete or widespread, and can involve mucous membranes as well as

	Differential diagnosis
Genital ulceration	Genital herpes (very common), chancroid, Bechet's syndrome, trauma
Palmar or plantar skin rash	Contact dermatitis, eczema, atopic dermatitis, erythema multiforme, Rocky Mountain spotted fever
Generalised skin rash	Systemic allergy, pityriasis rosea
Generalised lymphadenopathy	Mononucleosis syndrome, Hodgkin's lymphoma
Aseptic meningitis	Viral exanthem

Table 1: **Differential diagnosis of diseases that can mimic early syphilis, by manifestation**

epithelised skin: a factor that led to syphilis being referred to as the great imitator. When mucous membranes are involved, lesions can appear as highly infectious mucous patches and, in moist areas, might have an exuberant, verrucous appearance resembling warts and are referred to as condyloma lata. The rash of secondary syphilis can be widespread or localised; pustular, macular, popular, or scaly in appearance; and might mimic other dermatological processes including pityriasis rosea, psoriasis, drug eruptions. Symptoms such as malaise, myalgia, sore throat, headache, or low-grade fever are commonly detected. In addition to cutaneous manifestations, the presentation of secondary syphilis can also include diffuse lymphadenopathy, hepatosplenomegaly, hepatitis, nephrotic syndrome, and other symptoms that can be missed by clinicians who do not have a high index of suspicion, possibly related to failure to take a sexual history (eg, partner number and type) as part of evaluation of hard-to-characterise clinical manifestations. Without treatment the lesions of secondary syphilis can spontaneously resolve without scarring. Resolution of untreated manifestations of secondary syphilis can typically take weeks to several months.

After resolution of secondary manifestations, untreated syphilis enters a latent stage in which clinical manifestations are absent and the infection can only be detected through serological testing. To guide management, latent syphilis is further divided into early and late latent syphilis, a differentiation that affects treatment decisions and partner notification recommendations. Based on observations of the Oslo Study of Untreated Syphilis early in the 20th century, within a year or two after resolution of secondary manifestations of infection, about 25% of untreated people will have recurrent secondary manifestations and therefore once again be potentially infectious to sexual partners.[22,23] Most recurrent clinical manifestations in early latent syphilis occur during the first year of latency.

After a period of years or even decades, based on data from the preantibiotic era,[22] about a third of people with untreated latent syphilis will have further clinical manifestations as either late neurosyphilis (general paresis or tabes dorsalis), cardiovascular syphilis, or gummatous syphilis. Cardiovascular syphilis most often manifests as aneurysm formation of the ascending aorta, aortic valve insufficiency, or coronary artery disease. Gumma (which could occur in virtually any location) are reactive, granulomatous processes that lead to symptoms as a result of their mass effect or local inflammation. In the latter part of the 20th century, cardiovascular and gummatous syphilis have become very rare.

Neurological involvement in syphilis

Neurosyphilis is a feared but poorly understood complication of infection that can occur at any time during the course of infection.[20,24] *T pallidum* and cerebrospinal fluid (CSF) abnormalities can be detected in the CNS in a substantial proportion of patients with early syphilis, many of whom do not have obvious neurological signs or symptoms.[25,26] The importance of invasion and its impact on therapeutic decision making, particularly in the earlier stages of infection remains a subject of debate and ongoing research. In the preantibiotic era, cerebrospinal fluid (CSF) abnormalities detected at the time of lumbar puncture were used to determine the duration of therapy.[27] Now there is little evidence that the presence of CSF abnormalities affect therapeutic outcomes for patients with early syphilis treated with long-acting penicillin.[23] In later stages, CSF abnormalities in asymptomatic infected individuals are believed to identify those at increased risk for clinical neurosyphilis who require more intensive therapy.

Clinical neurosyphilis can manifest in a range of ways that roughly correlate with duration of infection, although some findings such as ocular involvement (uveitis, cranial nerve palsies, etc) might occur throughout the course of untreated syphilis.[24] Some individuals with secondary syphilis might present with an aseptic meningitis syndrome of headache and mild meningismus (syphilitic meningitis). The classic indication proposed by Merritt and colleagues[24] was that severe syphilitic meningitis was a relatively uncommon form of neurosyphilis; however, more contemporary studies suggest that mild meningeal signs and symptoms might be present in more than 40% of people with secondary syphilis[26] and, like other secondary manifestations of infection, can resolve with or without therapy. Later in the natural history of untreated syphilis, inflammation of small and medium CNS arteries might result in stroke or premonitory stroke-like manifestations of meningovascular syphilis, occurring several years (typically 5–10 years, although possibly earlier in patients with HIV) after infection. Recognition of meningovascular syphilis in relatively young people presenting with premonitory signs or symptoms of meningovascular syphilis provides an opportunity for treatment to prevent additional, irreversible neurological deficits due to stroke. The most common manifestations of meningovascular syphilis are hemiplegia, aphasia, or seizures related to involvement of the middle cerebral artery or its branches.[24]

Later in the course of untreated syphilis, chronic CNS infection might lead to general paresis or, less commonly,

tabes dorsalis.[20,24] from. General paresis is a cause of progressive dementia, which neuronal death, cerebral atrophy, and meningeal lymphocytic infiltration, and is reported to have accounted for up to 10% of psychiatric hospital admissions in the pre-antibiotic era. Clinical manifestations of paresis include dementia, seizures, and a wide variety of psychiatric syndromes. Merritt and colleagues[24] reported that patients with general paresis uniformly have abnormal CSFs with elevation of CSF white blood cells (WBCs), an elevated CSF protein concentration, and abnormal CSF serological tests for syphilis (the Wasserman test was used at the time). When diagnosed, the goal of therapy for recognised general paresis is to halt clinical progression, but reversal of neurological deficits is less common. In the latter part of the 20th and beginning of the 21st centuries, general paresis has become rare.

The other clinical manifestation of late neurosyphilis, tabes dorsalis, appears to result from involvement of nerves of the posterior columns and spinal nerve roots.[22,24] Early tabes typically presents as lightning pains, which occur as abrupt, severe, unprovoked radicular pain and symptoms of ataxia reflecting loss of proprioception. On physical examination, pupillary abnormalities including the Argyll Robertson pupil, loss of reflexes, and impaired vibratory sense are common.[24] Although usually occurring as the result of changes to the long nerves in the leg, these painful episodes can occur at nearly any site, including the abdomen to cause so-called visceral crises. Like general paresis, tabes dorsalis has become uncommon in the antibiotic era.

Diagnosis

Sustained culture of *T pallidum* is difficult and usually used only in research. Animal models, most often using rabbit inoculation, have been valuable for isolation of *T pallidum*, as well as to study host response to infection.[28] Direct detection of *T pallidum* from lesion exudate collected from patients with primary and secondary syphilis is preferable, but these tests are not readily accessible in many settings. Darkfield microscopy has traditionally been used for detecting *T pallidum*; however, neither darkfield microscopes nor the expertise to use them are widely available.[29] Alternatives for direct detection of *T pallidum* include fluorescence microscopy and nucleic acid amplification (PCR); however, these tests are also not readily available and are not widely used.[29]

Serological testing is the most common method for syphilis screening, diagnosis, and follow-up of treatment.[29] Test performance factors such as sensitivity, specificity, predictive values, and reproducibility impact, can vary depending on the purpose of the test. A useful starting point in serological test interpretation is to review the reason for testing and the desired use of test results. Thus, in situations such as screening, in addition to sensitivity, the consequences of misidentifying a person as infected (or not) become important for test selection and interpretation; whereas when serology is used for diagnosis, test sensitivity becomes a major consideration. When used to assess response to therapy, test-to-test reproducibility and the anticipated time-course of response to therapy become important considerations.

Two different types of tests are used, typically in sequence, one to identify individuals with possible infection and then a second, unrelated confirmatory test to validate results and reduce false positives.[29] So-called non-treponemal tests for syphilis are based on antigens synthesised from lecithin, cholesterol, and cardiolipin reacting with antibodies produced in response to *T pallidum* infection.[29] Prototypic non-treponemal tests include the rapid plasma reagin and venereal disease research laboratory (VDRL) tests, which detect both IgG and IgM antibodies. Antibody titres detected using these tests roughly correspond with the stage of disease,[28–30] increasing throughout primary infection and peaking late in the secondary or in the early latent stages of infection. Thus, even without therapy, non-treponemal antibody titres can gradually decline spontaneously and, in some patients, become non-reactive. Non-treponemal tests can also provide quantitative information on changes in antibody concentrations, making them helpful to assess response to therapy.[31,32] After successful therapy, antibody titres will decline in most but not all patients, with response being faster in people with earlier stages of disease and higher test titres at the time of treatment. For patients with early syphilis, two-dilution (four-fold) declines in serological test titres occur in most patients within 3–6 months of treatment. Previous syphilis infection does not considerably delay serological response to therapy. After therapy, about 15–20% of successfully treated patients will be serofast and not show a two-fold or greater decline in non-treponemal test titres even 12 months after treatment.[17,33] In most of these patients retreatment does little to promote further decline in serological therapy.[34] Patients with late latent syphilis and lower test titres are more likely to be serofast after recommended therapy.[29]

Treponemal tests, which detect antibodies to treponemal antigens, are also commonly used. In the past, these antigens were generated by propagation of *T pallidum* in animals, but more recently molecularly-cloned antigens have been used to develop low-cost, sometimes automated, serological tests for syphilis.[29] Previous tests include fluorescent treponemal antibody adsorbed (FTA-ABS) tests and *Treponema pallidum* particle agglutination (TPPA), but cheaper, easier to perform, and automatable treponemal tests such as enzyme immunoassays have become far more widely used. Irrespective, treponemal tests tend to be qualitative, rather than quantitative, but often remain positive for life, despite successful therapy and, therefore, are not helpful for evaluation of response to therapy.

False-positive tests for syphilis can lead to unnecessary treatment, anxiety, and stigmatisation of individuals who do not have syphilis.[29,35] False-positive non-treponemal tests are more common in patients with rheumatological diseases (eg, systemic lupus erythematosus), pregnancy, chronic infections (eg, infective endocarditis, HIV, and chronic mycobacterial disease), parenteral drug use, and other disorders that tend to generate high circulating immunoglobulin levels.[29] So-called biological-false-positive non-treponemal tests can also occur in about 1% of the general population in individuals who do not have recognised predisposing factors. The prevalence of, and factors associated with, false-positive treponemal tests when the treponemal tests are done first are less well defined. In one study of more than 140 000 patients,[36] 2743 (57%) of the 4834 individuals with initially positive treponemal tests had non-reactive rapid plasma reagin tests and nearly 866 (18%) seemed to have falsely positive results. The rates of treponemal enzyme immunoassays tests that could not be confirmed with further non-treponemal or treponemal testing were higher among patients from populations judged to have a low prevalence of syphilis than among those from high-prevalence groups. As a result, when syphilis testing is first done with treponemal tests, the US CDC now recommends doing a second unrelated treponemal test in patients whose non-treponemal test is negative.

As the costs have decreased and the ease of treponemal tests have increased, so-called reverse algorithm testing has become more widely used in which a treponemal test is used initially, followed by a non-treponemal assay for confirmation in patients with a positive first test.[36,37] This approach has proven highly effective for screening low-prevalence populations, but is of questionable value when used for individuals with a history of syphilis or in populations with a relative high prevalence of syphilis due to the frequent detection of persisting treponemal antibodies.

In recent years, rapid (<30 min), inexpensive, point-of-care tests have become available, which can be used outside of routine laboratory settings on whole blood, serum, or plasma. Most tests use treponemal antigens and have permitted increased testing, proving particularly helpful for prenatal screening as part of efforts to prevent congenital syphilis in LMICs and in settings such as urgent care that otherwise rely on syndromic diagnosis to guide management decisions.[3,38]

Diagnosis of neurosyphilis

Because neurosyphilis can be asymptomatic or present in many different ways, analysis of CSF is often helpful to confirm its presence. However, lumbar puncture and CSF analysis are presently only recommended for diagnosis of neurosyphilis in individuals with appropriate clinical syndromes, for evaluation of possible treatment failures, and for some patients with latent syphilis.[23] In these situations, a reactive CSF VDRL test is diagnostic of neurosyphilis, while detection of an elevated CSF white blood cell count (typically predominantly lymphocytes) or an elevated CSF protein (which can be seen without a reactive CSF VDRL test) in patients with untreated syphilis might provide support for a neurosyphilis diagnosis. In patients with chronic HIV infection, differentiation between CSF lymphocytosis due to HIV and that due to syphilitic involvement of the CNS can be difficult, although CNS lymphocytosis due to HIV rarely exceeds 20 cells per mm^3. In patients with suspicion of neurosyphilis but a negative CSF VDRL, a CSF FTA-ABS test can be used to rule out neurosyphilis.[24] Although the rapid plasma reagin and VDRL tests can be used interchangeably on serum specimens, rapid plasma reagin testing on CSF is not recommended. Research is continuing to evaluate other possible markers of neurosyphilis.

Management

Penicillin has long been the drug of choice for treatment of syphilis. In recent years, manufacturing shortfalls have sometimes limited the availability of benzathine benzylpenicillin, the preferred formulation for most syphilis therapy.[39] Long-acting formations of benzathine benzylpenicillin are the most commonly recommended drugs for syphilis treatment. Alternate therapy using multiple doses of procaine penicillin, doxycycline, or ceftriaxone can be used when intravenous therapy might be difficult or in the case of possible penicillin allergy (table 2).[23,38,40] For early (primary, secondary, or early latent) syphilis, a single injection of 2·4 million units of benzathine benzylpenicillin is recommended. For patients with late or unknown-duration latent syphilis, recommended therapy is injections of 2·4 million units of benzathine benzylpenicillin weekly for 3 successive weeks.[23,38,40] For patients with neurosyphilis, recommended treatment is higher doses (18–20 million units per day in divided doses) of intravenous aqueous penicillin G administered every 4 h for 10–14 days, and some experts recommend two to three doses of benzathine benzylpenicillin after completion of intravenous therapy to mirror the duration of therapy for late infections. Treatment of patients with syphilis who have a proven penicillin allergy can be challenging. Fluoroquinolone, sulphonamides, and aminoglycoside antibiotics are not effective. Doxycycline or tetracycline given for 14–28 days depending on the stage of infection can be used for treatment of non-pregnant patients with beta-lactam-antibiotic allergy, but there are concerns related to the possibility of medication non-adherence with the prolonged course of antibiotics. There are no recommendations to modify therapy for pregnant women or for patients with HIV infection. For treatment of syphilis in pregnancy, there are no recommended alternate regimens for women with penicillin allergy and desensitisation to penicillin is recommended. Azithromycin was evaluated as a promising alternative to

	Penicillin-sensitive patients	Penicillin-allergic patients
Primary, secondary, and early latent syphilis (<1 year); epidemiological treatment for contacts	Total of 2·4 million units of penicillin; single intramuscular dose of two injections of 1·2 million units in one session	Doxycycline 100 mg twice a day or tetracycline 500 mg four times a day, given orally for 14 consecutive days
Late latent (>1 years) or when CSF was not examined in latency; cardiovascular syphilis; late benign (cutaneous, osseous, or visceral) gumma	Total of 7·2 million units of penicillin intramuscularly in doses of 2·4 million units at 7 day intervals over a 21 day period	Doxycycline 100 mg twice a day or tetracycline 500 mg four times a day, given orally for 28 consecutive days
Symptomatic or asymptomatic neurosyphilis	2–4 million units aqueous (crystalline) penicillin G intravenously every 4 h for at least 10 days; 2–4 million units procaine penicillin intramuscularly daily and probenecid 500 mg orally four times a day for 10–14 days	Ceftriaxone 2 g intramuscular or intravenously daily for 10–14 days (cross-sensitivity with penicillin is rare but does occur; alternative regimen should be discussed with a specialist)

As recommended by the US Public Health Service. CSF=cerebrospinal fluid.

Table 2: **Recommended treatment for syphilis**[23,38]

beta-lactam antibiotics; however, strains carrying a 23S rRNA mutation for macrolide resistance,[41,42] first described over 30 years ago, are now prevalent and azithromycin and other macrolide regimens are no longer recommended for syphilis treatment unless there are no suitable alternatives and robust follow-up can be assured.[43,44]

After syphilis treatment, 30–50% of treated patients have a Jarisch-Herxheimer reaction characterised by fever, myalgia, and possible intensification of skin rash. This reaction, which has recently been associated with serological response to syphilis therapy, is sometimes mistaken for a drug reaction but will resolve spontaneously in less than 24 h with mild supportive care (hydration and over the counter antipyretics). Because benzathine benzylpenicillin leads to circulating levels of penicillin for longer than a week, on those occasions when patients with late or unknown duration latent syphilis return for continued therapy within 12–14 days of their last injection, the recommended series of injections need not be restarted.[23,38]

Response to therapy

Response to therapy is indicated by a two (four-fold) or more dilution decline in non-treponemal serological test titres or, if initial titres are positive at a 1:1 or 1:2 dilution, by becoming non-reactive.[23,31,32] However, serological response to therapy is not universal in successfully treated patients and 15–20% of patients with early syphilis might have so-called serofast titres, which do not change substantially (ie, remain positive at the initial titre or only decline a single dilution).[17,33] Clinical experience suggests that few of the patients who remain serofast after therapy benefit from further therapy.[34] A meaningful serological response to therapy is more likely if patients are younger, have earlier stages of disease, have higher serological test titres at the time of diagnosis, or experience a Jarisch-Herxheimer reaction.[33,34] The serological response to therapy for patients with latent and more longstanding infections is less well described, but it seems to be gradual and the proportion of patients who remain serofast after therapy seems higher than for early syphilis.

Monitoring of response to therapy in neurosyphilis can be challenging and there have been few formal studies of its efficacy because of difficulties in getting follow-up lumbar punctures. A serological response to therapy using the rapid plasma reagin test is highly predictive of resolution of both neurological and CSF abnormalities.[45] When follow-up CSF studies are available, the white blood cell count is the earliest variable to respond, whereas a reactive CSF VDRL test can take years to change, and additionally could be slower in individuals with HIV.[46] CSF protein determination in individuals with neurosyphilis is both non-specific and can be slow to resolve.

Control strategies

Beyond primary prevention using avoidance strategies and condoms, approaches for control of diagnosed syphilis are based on adaptation of recommendations made by US Surgeon General, Thomas Parran: widespread testing (screening), professional and public education and engagement, timely treatment, and continuing research to improve these efforts.[19] In LMICs, syphilis management is most often started after presentation for evaluation of genital ulceration or as a result of prenatal care testing.[38] In North America and western Europe, in addition to infections detected as part of syndrome evaluation or prenatal care, infections are commonly detected through screening during usual care, particularly at-risk populations or blood donors.

Notification and partner management strategies

Other than for congenital syphilis, transmission of syphilis is thought to be transmitted almost entirely by individuals with early stage infection. For such patients, administration of preventive therapy (2·4 million units of benzathine benzylpenicillin administered parenterally) is recommended for all recent (30–90 days) sexual partners.[23] Since lesions have not been present for some time in individuals with later latent syphilis (ie, latent syphilis of more than 1–2 year duration),[23,38] preventive therapy is not recommended for partners, although

serological testing to detect otherwise unapparent syphilis is recommended.

Conclusion and future research

Research is continuing into *T pallidum* biology and host response to infection as part of efforts to develop vaccines for syphilis prevention.[46] At present, understanding for and the principles used to guide syphilis management are based on data collected in the pre-penicillin era when the disease was far more common than it is today. The clinical and prognostic significance of CNS invasion by *T pallidum* in patients with early syphilis and associated CSF abnormalities remains an area of great controversy. Similarly, since the initial studies of penicillin therapy for syphilis, changes in formulations and refinement of serological testing have raised questions as to the optimum medication dose, duration of therapy, and assessment of serological response to therapy. Questions also continue about the interpretation, evaluation, and management of the substantial proportion of patients who remain serofast. Carefully designed clinical trials are needed to answer these recurring questions.

Syphilis remains an important public health problem that is regularly encountered by clinicians working in a range of settings. It remains common in LMICs and rates are increasing in higher-income countries, particularly among MSM. Without a high index of suspicion and familiarity with the infection's protean manifestations, syphilis diagnosis is sometimes missed.

Declaration of interests

I declare no competing interests.

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References

1 Brandt AM. No Magic Bullet: A social history of venereal disease in the United States since 1880. New York: Oxford University Press, 1985.
2 Newman L, Rowley J, Hoorn SV, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One*: doi; 10.1371/journal.pone.0143304.
3 WHO. Report on global sexually transmitted infection surveillance 2015. Geneva: World Health Organization, 2016
4 Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2014. Atlanta: US Department of Health and Human Services, 2015.
5 Public Health England. Infection Report: Sexually Transmitted Infections. London: Public Health England, 2015.
6 Sparling PF, Swartz MN, Musher DM, Healy BP. Clinical Manifestations of syphilis. In: Holmes KK, Sparling PF, Stamm WE, et al, eds. Sexually Transmitted Diseases, fourth edn. New York: McGraw Hill, 2008: pp 661–84.
7 Hutchinson CM, Rompalo AM, Reichart CA, Hook EW III. Characteristics of patients with syphilis patients attending Baltimore STD clinics: multiple high risk subgroups and interactions with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151:** 511–16.
8 Phipps W, Kent CK, Kohn R, Klausner JD. Risk factors for repeat syphilis in men who have sex with men, San Francisco. *Sex Transm Dis* 2009; **36:** 331–35.
9 Centers for Disease Control and Prevention. Notes from the field: Repeat syphilis infection and HIV coinfection among men who have sex with men—Baltimore, Maryland, 2010–2011. *MMWR Morb Mortal Wkly Rep* 2013; **62:** 649–50.
10 Grassly NC, Fraser C, Garnett GP. Host immunity and synchronized epidemics of syphilis across the United States. *Nature* 2005; **433:** 417–21.
11 Darrow WW, Echenberg DF, Jaffe HW, et al. Risk factors for human immunodeficiency virus (HIV) infection in homosexual men. *Am J Public Health* 1987; **77:** 479–83
12 Hook EW III. Syphilis and HIV infection. *J Infect Dis* 1989; **160:** 530–34.
13 Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and the acquisition of HIV infection in homosexual men. *JAMA* 1988; **260:** 1429–33.
14 Peterman TA, Newman DR, Maddox L, Schmitt K, Shiver S. High risk for HIV following syphilis diagnosis among men in Florida, 2000-2011. *Public Health Rep* 2014: **129:** 164–69.
15 Pathela P, Braunstein SL, Blank S, Shepard C, Schillinger JA. The high risk of HIV diagnosis following a diagnosis of syphilis: a population-level analysis of New York City men. *Clin Infect Dis* 2015; **61:** 281–87.
16 Hutchinson CM, Hook EW III, Shepherd M, Verley J, Rompalo AM. Altered clinical presentations and manifestations of early syphilis in patients with human immunodeficiency virus infection. *Ann Intern Med* 1994; **121:** 94–99.
17 Rolfs RT, Joesoef MR, Hendershot EF, et al. The syphilis and HIV Study Group. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. *N Engl J Med* 1997; **337:** 307–14.
18 Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev* 2014; **27:** 89–115.
19 Parran T. Shadow on the Land. Syphilis. New York: Reynal and Hitchcock, 1937.
20 Hook EW III, Marra CM. Acquired syphilis in adults. *N Engl J Med* 1992; **326:** 1060–69.
21 Mertz KJ, Trees D, Levine WC, et al. Etiology of genital ulcers and prevalence of human immunodeficiency virus coinfection in 10 US cities. *J Infect Dis* 1998; **178:** 1795–98.
22 Gjestland T. The Oslo study of untreated syphilis: An epidemiologic investigation of the natural course of syphilitic infection based on a restudy of the Boeck-Bruusgaard material. *J Chronic Dis* 1955; **2:** 311–44.
23 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015; **64:** 1–137.
24 Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford University Press, 1946.
25 Chesny AM, Kemp JE. Incidence of *Spirochaeta pallidum* in cerebrospinal fluid during the early stages of syphilis. *JAMA* 1924; **22:** 172–78.
26 Lukehart SA, Hook EW III, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med* 1988; **109:** 855–62.
27 Moore JE, Kemp JE, Eagle H, Padget P, Goodwin MS. The Modern Treatment of Syphilis. Springfield: CC Thomas, 1941.
28 LaFond RE, Lukehart SA. Biological basis for syphilis. *Clin Microbiol Rev* 2006; **19:** 29-49.
29 Larsen SA, Pope V, Johnson RE, Kennedy EJ. A manual of tests for syphilis. Washington, DC: American Public Health Association; 1998, pp 1–47.
30 Holman KM, Hook EW III. Clinical management of early syphilis. *Expert Rev Anti Infect Ther* 2013; **11:** 839–43.
31 Brown ST, Zaidi A, Larsen SA, Reynolds GH. Serological response to syphilis treatment. A new analysis of old data. *JAMA* 1985; **253:** 1296–99.
32 Romanowski B, Sutherland R, Fick FH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. *Ann Intern Med* 1991; **114:** 1005–10.
33 Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and the serofast state after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis* 2011; **53:** 1092–99.
34 Sena AC, Wolff M, Behets F, et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. *Clin Infect Dis* 2013; **56:** 420–22.

35 Thomas DL, Rompalo AM, Zenilman J, Hoover D, Hook EW III, Quinn TC. Association of hepatitis C virus infection with false-positive tests for syphilis. *J Infect Dis* 1994; **170:** 1579–81.

36 Centers for Disease Control and Prevention. Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006–2010. *MMWR Morb Mortal Wkly Rep* 2011; **60:** 133–37.

37 Sena AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. *Clin Infect Dis* 2010; **51:** 700–08.

38 WHO. Guidelines for the Treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization, 2016.

39 WHO. Addressing global shortages of medicines, and the safety and accessibility of children's medication. Geneva: World Health Organization, 2015.

40 Kingston M, French P, Higgins S, et al. UK National Guidelines on the Management of Syphilis 2015. *Inter J STD AIDS* 2008; **19:** 729–40.

41 Hook EW III, Martin DH, Stephens J, Smith BS, Smith K. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. *Sex Transm Dis* 2002; **29:** 486–90.

42 Reidner G, Rusizoka M, Todd, et al. Single-dose azithromycin verses penicillin benzathine for the treatment of early syphilis. *N Engl J Med* 2005; **353:** 1236–44.

43 Stamm LV, Bergen HL. A point mutation associated with bacterial macrolide resistance is present in both 23S rRNA genes of an erythromycin resistant *Treponema pallidum* clinical isolate. *Antimicro Agents Chemother* 2000; **44:** 806–07.

44 Lukehart SA, Gordornes C, Molini, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* 2004; **351:** 154–58.

45 Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma regain titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis* 2008; **47:** 893–99.

46 Gottlieb SL, Deal CD, Giersing B, et al. The global roadmap for advancing development of vaccines against sexually transmitted infections: update and next steps. *Vaccine* 2016; **34:** 2939–47.