

Contemporary clinical aspects of syphilis, diagnosis and treatment

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SYPHILIS HAS BEEN PRESENT in the Western world since the Middle Ages, although its origins continue to be a matter of debate. It is caused by infection with the spirochaete *Treponema pallidum* subsp. *pallidum*. Its high level of infectivity and protean clinical manifestations ensure its special place in the history of Western medicine. Serological testing was developed in the early part of the 20th century and suggested that at that time about 10% of adults in cities such as Paris, Berlin and New York were infected with the disease.¹ Although syphilis became a rarity in many Western countries after the development of penicillin, its transmission still occurred in some social settings, such as rural and remote Australian Indigenous communities, the urban poor in the southern United States, and inner city communities of homosexually active men across the Western world. Even though the long-term sequelae of syphilis are now rare, the disease has increased importance in the era of HIV, as genital ulceration may increase the risk of HIV acquisition.^{2,3}

Abstract

- ◆ Even though it had become almost forgotten in the developed world, syphilis, caused by infection with the spirochaete *Treponema pallidum* subsp. *pallidum*, is now resurgent.
- ◆ Most diagnoses are made serologically, but can also be made by direct detection of the organism from clinical specimens. An enzyme immunoassay has become the most commonly used screening test in Australia.
- ◆ Appropriate treatment of any stage of syphilis is intended to prevent progression to later stages of disease.
- ◆ Although oral therapy with azithromycin and tetracyclines has been investigated, parenteral treatment remains the standard of care.

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Epidemiology

Syphilis affects both men and women. The World Health Organization estimated that in 1995 there were 12 million cases of venereal syphilis.⁴ Most of these occurred in the developing world. Although disease incidence in developed countries has waned since the advent of penicillin some 60 years ago, there has been a recent resurgence of the disease, predominantly among men who have sex with men.⁵⁻¹⁰

Transmission occurs after contact with infective lesions and body fluids. Lesions occur on the genitalia, in the mouth and oral cavity, or, less commonly, on the breasts or other locations. Transmission can also occur in utero or at delivery, from transfused blood or via accidental inoculation while handling infected clinical material.

Pathophysiology and microbiology

T. pallidum subsp. *pallidum* is the causative organism of syphilis. Other subspecies of *T. pallidum* cause the diseases yaws, pinta and endemic syphilis. These organisms are very closely related to *T. pallidum* subsp. *pallidum* and, although they produce different clinical manifestations, infections caused by these organisms are serologically indistinguishable from syphilis. Non-pathogenic treponemes also inhabit the human oral cavity. In-vitro culture of *T. pallidum* has not been achieved, making study of the organism difficult. Only animal models in which testes of virgin New Zealand white rabbits have been inoculated have made studies of pathogenesis




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Illustrative cases

Patient 1

Sanjay is a 42-year-old man with chronic HIV-associated thrombocytopaenia. His CD4 count was 260×10^6 cells/L (T cell count suggestive of mild/moderate immune suppression) and he had low-level HIV viraemia (2390 copies/mL). He presented with a widespread macular rash and lymphadenopathy. His rapid plasma reagin (RPR) level was 64 and he was treated with a single dose of intramuscular benzathine penicillin (1.8 g). The rash and lymphadenopathy resolved. However, over subsequent weeks he began to experience balance problems. He felt as though he was "walking on cotton" and had a wide-based gait and a positive Romberg sign. His RPR was 128 at this time. Examination of the cerebrospinal fluid was precluded by thrombocytopaenia. He was admitted to hospital for intravenous therapy for early neurosyphilis. At his hospital admission he was found to have cholestatic liver enzymosis. Investigations for other causes of liver function abnormalities were negative. The liver function and neurological abnormalities and elevated RPR all improved with a 14-day course of benzylpenicillin (1.8 g every 4 hours). His RPR of 16 at 3-month follow-up suggests a satisfactory initial response with a fall of two dilutions, but he will be followed to ensure that the RPR falls further.

Patient 2

Simon, a 35-year-old office worker, complained of a sore throat persisting for 2 weeks. He had also experienced fever, myalgia and a non-pruritic rash, but these symptoms had resolved. He had no genital lesions. There was a raised fleshy circular lesion of 2.5 cm diameter on the right side of his pharynx. This was an oral mucous patch. He had a childhood history of desquamation after oral penicillin treatment. He was given penicillin desensitisation and treated with a single dose of intramuscular benzathine penicillin. The oral lesion resolved within a day. His RPR level was 128 and *Treponema pallidum* particle agglutination assay was positive. An HIV test was negative. He had been practising unprotected receptive orogenital sex, as he knew that this conferred a lower risk of HIV infection.

most chancres heal in 2 weeks, although this may take longer in immunocompromised hosts. Treatment speeds resolution and prevents progression of disease.

In the absence of treatment, dissemination of the organism becomes clinically apparent 4–10 weeks after the appearance of the primary lesion. Treponemes can be found in many organs, including the blood, lymph nodes, skin and central nervous system. A florid immune response occurs in this secondary stage of the infection. Without treatment, this stage lasts an average of 3.6 months.¹³ Relapse of untreated disseminated disease may occur in the first 4 years following infection.¹⁴ Again, antibiotic treatment brings rapid resolution to the symptoms and signs of secondary disease and prevents disease progression.

Resolution of disseminated disease is followed by a phase of latent infection, only detectable serologically. One third of untreated patients will go on to develop long-term sequelae.¹⁴ These may manifest as cardiovascular, gummatous or central nervous system disease. Obliterative endarteritis is the pathologic hallmark of cardiovascular disease, which manifests after decades as aortic regurgitation, coronary ostial stenosis and aortic aneurysms. Gummas develop most commonly in the skin, liver, spleen and in bones. They are variable in size and inflammatory in nature. Central nervous system disease may involve chronic meningitis, cerebral gummas, neuronal loss in the central cortex (paretic neurosyphilis) or loss of axons and myelin in the dorsal columns of the spinal cord (tabes dorsalis).¹⁵

Congenital syphilis occurs most commonly with early syphilitic infection in the mother during pregnancy. It may result in intrauterine or perinatal death. Early signs in the neonate include a desquamating rash, hepatomegaly and bony abnormalities. Later signs include notched teeth, visual loss due to interstitial keratitis and eighth nerve deafness.¹⁵

Clinical manifestations

Clinical manifestations can be split into early and late disease, which is useful for determining appropriate therapy. Early disease refers to the first 2 years after infection and includes both primary and secondary syphilis. Late disease refers either to tissue destructive phases that do not occur until years after the incident infection or to asymptomatic latency more than 2 years after infection.

Primary disease is manifest by the chancre. This occurs at the site of inoculation. Initially a papule, it undergoes central erosion, leaving an indurated edge with a smooth base and no exudate. Atypical lesions may occur and lesions in the cervix or anal canal will often go unnoticed. The differential diagnosis for genital ulcers includes herpes, chancroid, lymphogranuloma venereum, Donovanosis, mycobacterial infection, trauma, tumours of the skin, autoimmune disease and drug eruptions. Primary disease may be asymptomatic.

possible.¹¹ The complete genome of the organism was published in 1998, and is notable for its small size, lack of transposable elements and paucity of metabolic elements.¹²

T. pallidum accesses the blood or lymphatic tissue through direct contact with either intact mucous membranes or abraded skin. Dissemination is rapid and widespread. The primary lesion occurs at the site of inoculation and is referred to as a chancre. Chancres are usually single, but people infected with HIV are more likely to develop multiple lesions. Chancres may not develop in every case or may go unnoticed. The incubation period for development of primary disease is variable, but averages 25 days.¹³ Primary lesions have many treponemes and are highly infectious. Without treatment,

I Methods for diagnosis of syphilis at different stages of disease

	Direct detection	EIA	RPR	TPPA/ TPHA	FTA- ABS	CSF VDRL
Primary — early	+	–	+/-	+/-	+/-	–
Primary — later	+	+/-	+	+/-	+	–
Secondary	+	+	+	+	+	+/*
Latent	–	+	+/-	+	+	–
Treated disease	–	+	+/-	+	+	–
Tertiary	–	+	-/+ (low titre)	+	+	+*
Previous yaws/pinta	–	+	-/+	+	+	–
Congenital syphilis	+/-	+	+	+	+	+
Biologic false positive	–	-†	+	–	–	–

EIA = enzyme immunoassay. RPR = rapid plasma reagin. TPPA = *Treponema pallidum* particle agglutination assay. TPHA = *T. pallidum* haemagglutination assay. FTA-ABS = fluorescent treponemal antibody absorbed test. CSF VDRL = cerebrospinal fluid venereal disease research laboratory slide test. *CSF VDRL is highly specific for neurosyphilis but insensitive.¹⁷ † False positives are rare with the syphilis EIA.

Secondary disease presents in many different ways and is a differential diagnosis for infectious mononucleosis, aseptic meningitis, pyrexia of unknown origin, uveitis and lymphadenopathy with hepatosplenomegaly. Rash and fever is the most common presentation. The rash is typically widespread, non-pruritic and maculopapular; and its hallmark is being present on the palms and soles. Pustular lesions or raised lesions known as condylomata lata (in moist areas, such as axillae and perineal areas) may occur. Lymphadenopathy, constitutional symptoms and mucous patches are also common. Prominent early neurosyphilis appears more likely to occur in patients who are infected with HIV.¹⁶ Almost any organ system may be affected and produce symptoms.

Latent infection is, by definition, asymptomatic, although relapses of secondary syphilis may occur in the first 4 years after infection. Diagnosis during this phase is serological. For the purpose of treatment choice, latent disease within 2 years of incident infection is classified as early disease, and more than 2 years after infection is termed late latent syphilis.

Tertiary disease manifests as late neurosyphilis, cardiovascular syphilis or gummatous disease. The clinical features of late neurosyphilis result from chronic meningitis and are now very rarely seen in the developed world. Meningovascular disease results in focal neurological signs related to cerebral infarction. Paretic disease causes personality and intellect change, altered sensorium, hyperactive reflexes and pupillary changes. There is generally overlap between the two presentations. Syphilitic aortitis is seen in most cases of untreated syphilis, but is uncommonly symptomatic. Gummatous disease develops slowly and manifests with local tissue destruction. Penicillin usually provides a rapid response even though gummatous lesions contain few spirochaetes.

Congenital syphilis

Often there are no abnormal findings at birth, but subsequent findings are divided into early and late phases. Early phase disease features bony disease, hepatosplenomegaly, skin rash and snuffles. Late phase disease features oromaxillofacial abnormalities, bony abnormalities and interstitial keratitis.

Diagnosis

Sexual history is a key feature when accurate, although in venereology, “truth may be the first casualty” (paraphrased from Samuel Johnson). Diagnosis is most often made serologically, but can also be made by direct detection of the organism from clinical specimens. At the time of appearance of the primary lesion, serology is often negative, so direct detection can aid diagnosis at that point. Box 1 summarises diagnostic methods.

Direct detection

Chancres contain many spirochaetes and are suitable for providing specimens for direct detection, but it must be remembered by clinicians that they are highly infectious. Darkfield microscopy of slides pressed directly onto lesions has been used for many years, but sensitivity and specificity are highly operator-dependent and a darkfield microscope is needed. Direct fluorescent antibody testing provides improved sensitivity, but requires a fluorescent microscope. Nucleic acid amplification testing is becoming increasingly available and offers high sensitivity and specificity as long as dry swabs are used.^{18,19}

Serology

Most diagnoses are made serologically. An enzyme immunoassay (EIA) has replaced the rapid plasma reagin (RPR) as the most commonly used screening test in Australia. The EIA has the advantages of much lower rates of false positive results and the ability to be automated, potentially increasing throughput and reducing inter-operator variability. The RPR is used to provide a quantitative result against which treatment success or failure may be measured.

Non-treponemal tests such as the RPR and venereal disease research laboratory slide test (VDRL) exploit the reactivity of antibodies to phospholipids that develop after infection, and are used as screening tests. The titre of these tests wanes with treatment and with time.

Treponemal tests such as the *T. pallidum* particle agglutination assay (TPPA) and fluorescent treponemal antibody absorbed test (FTA-ABS) detect specific anti-

2 Appropriate treatments for syphilis at various stages of disease

Stage	Definition	Recommended treatment	Alternative treatment*
Early syphilis	Less than 2 years' duration (excluding early neurosyphilis)	Benzathine penicillin 1.8 g IM single dose	Doxycycline 100 mg orally twice daily for 14 days
Late latent syphilis	Asymptomatic; greater than 2 years' duration	Benzathine penicillin 1.8 g IM for 3 weekly doses	Doxycycline 100 mg orally twice daily for 28 days
Neurosyphilis	Early or late neurosyphilis	Benzylpenicillin 1.8 g every 4 hours IV for 14 days	Ceftriaxone 2 g (IV/IM) daily for 14 days
Tertiary syphilis — other forms	Cardiovascular or gummatous	Benzathine penicillin 1.8 g IM for 3 weekly doses	Doxycycline 100 mg orally twice daily for 28 days
Syphilis in pregnancy	Any stage	Treat mother for appropriate stage with penicillin	Desensitise if necessary
Congenital syphilis	All neonates of mothers with syphilis in pregnancy	Benzyl- or procaine penicillin 50 mg/kg (IV/IM) for 14 days	Ceftriaxone 75 mg/kg (IV/IM) daily for 14 days
Contact	Sexual contact with early syphilis	Benzathine penicillin 1.8 g IM single dose	Doxycycline 100 mg orally twice daily for 14 days

IM = intramuscular. IV = intravenous. *These protocols may be inferior to the recommended therapy. Seek specialist advice for alternative treatment regimens, particularly in pregnancy and childhood.

treponemal antibodies and are especially useful in the diagnosis of late syphilis (where non-treponemal tests may be negative) and in clarifying whether positive non-treponemal tests are true positives. The EIA detects antibodies to recombinant treponemal proteins. It has become widely used as a screening test. Once they are positive, treponemal tests generally remain positive for life.

Rapid tests are in development. Fingerprick blood is usually appropriate. These tests use an immunochromatographic method and are designed to be read within 30 minutes.

False positive non-treponemal tests may occur in the setting of other infections, such as rickettsial disease, HIV, bacterial endocarditis, hepatitis C and bacterial pneumonia; or with pregnancy or inflammatory disease such as systemic lupus erythematosus. Treponemal tests will be negative in these circumstances.

Neurosyphilis

The central nervous system is frequently invaded during early syphilis, but symptomatic disease is uncommon, especially in people not infected with HIV. Neurosyphilis is diagnosed on the basis of clinical signs and examination of the cerebrospinal fluid. In the absence of clinical signs, asymptomatic neurosyphilis is diagnosed when the cerebrospinal fluid (CSF) exhibits pleocytosis, elevated protein, decreased glucose or positive VDRL. Contamination of the CSF with blood at lumbar puncture can make interpretation of a positive VDRL challenging. Formulas are available to assist with detection of immunoglobulin formed in the central nervous system,²⁰ but repeat collection may be more reliable.

Congenital syphilis

A mother's positive serology at delivery suggests congenital syphilis. Babies suspected of having congenital syphilis should be examined and undergo IgM, IgG EIA and VDRL tests after delivery. IgG may be unreliable because of passage of maternal antibodies. Infants with probable congenital syphilis should have CSF examination for CSF VDRL. Direct detection methods are highly specific. All infants with diagnosed and suspected congenital syphilis should undergo subsequent serological follow-up.²¹

Treatment

Appropriate treatment of any stage of syphilis is intended to prevent progression to later stages of disease. Guidelines vary because there have been relatively few head-to-head comparisons of treatment strategies. While oral therapy with azithromycin and tetracyclines has been investigated, parenteral treatment remains the standard of care because of treatment failure due to macrolide resistance and the uncertainty of treatment adherence for patient-administered oral dosing over 2–4 weeks.^{22,23}

Treatment protocols differ for the different stages of disease (Box 2).

Relapse is well described after treatment for neurosyphilis. Relapse after treatment for early disease can be indistinguishable from reinfection. Because of the risk of relapse and potential for serious sequelae, all patients treated for syphilis should undergo serological and clinical follow-up. It is recommended to repeat quantitative non-treponemal tests 3, 6

and 12 months after treatment for early syphilis; after 2 years for late latent disease; and 6-monthly after neurosyphilis until all parameters normalise.²⁰

Patients with secondary syphilis have many organisms spread throughout the body. A Jarisch–Herxheimer reaction, with chills, fever, rash, tachycardia and vasodilatation, may occur with treatment initiation as spirochaetes are killed. Administration of oral prednisone (25 mg single dose) with the first dose of antitreponemal therapy can prevent this.

Empiric treatment (appropriate for early disease) of sexual partners of patients with infectious syphilis is recommended, as early syphilis is highly contagious.

Syphilis and HIV

The diagnosis of syphilis is an indication for testing for HIV and other sexually transmitted infections. In the setting of HIV infection, the clinical presentation of syphilis and response to treatment may be altered. Immune control of syphilis is modulated by cellular immune responses. Untreated HIV infection is likely to modify the immune response to *T. pallidum* infection. Multiple chancres or simultaneous primary and secondary disease are more likely to occur.^{24,25} Transient alterations in the HIV viral load and CD4 cell count have been reported with incident syphilis infection,²⁶ but the significance of this is unclear. Serologically defined treatment failure is reported to be higher in the setting of coinfection,²⁷⁻²⁹ although there are no published data confirming increased risk of clinical treatment failure with concomitant HIV infection. Treatment of syphilis in patients infected with HIV is the same as in those without HIV, but careful follow-up is required because of the reports of serological failure in this setting. Some clinicians choose to increase the intensity of therapy in this setting.

Role of lumbar puncture

The central nervous system is commonly invaded by treponemes during early syphilis,²⁹ but few people go on to develop symptomatic late neurosyphilis despite the fact that recommended regimens do not produce treponemicidal levels of penicillin in the central nervous system.^{30,31} CSF analysis is recommended in patients with symptoms suggestive of neurosyphilis and in patients treated for neurosyphilis. In the latter group, CSF analysis is indicated to evaluate for treatment outcome, as treatment failures in neurosyphilis are well described. Some authorities suggest that HIV-infected patients with late latent syphilis should have CSF analysis to diagnose asymptomatic neurosyphilis,³² although guidelines from the US Centers for Disease Control and Prevention suggest it is optional.¹⁷ Patients with RPR titres ≥ 32 are more likely to have CSF parameters consistent with neurosyphilis, and a case can be made for performing a lumbar puncture on

all HIV-infected patients with an RPR ≥ 32 , irrespective of whether neurological symptoms are present.^{33,34}

Conclusions and recommendations

Even though it had become almost forgotten in the developed world, syphilis is now resurgent. Diagnosis depends on clinical recognition of the protean manifestations of the disease. William Osler said 110 years ago, “Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you”. Challenges remain. These include control of the current epidemic; development of rapid testing, especially for antenatal and sexual health clinics and resource-constrained settings; serological testing that is more accurate and more predictive; more practical drug sensitivity assessment; development of oral therapy; and a safe, effective vaccine. A core remaining question is whether eradication of syphilis is possible.

Competing interests

None identified.

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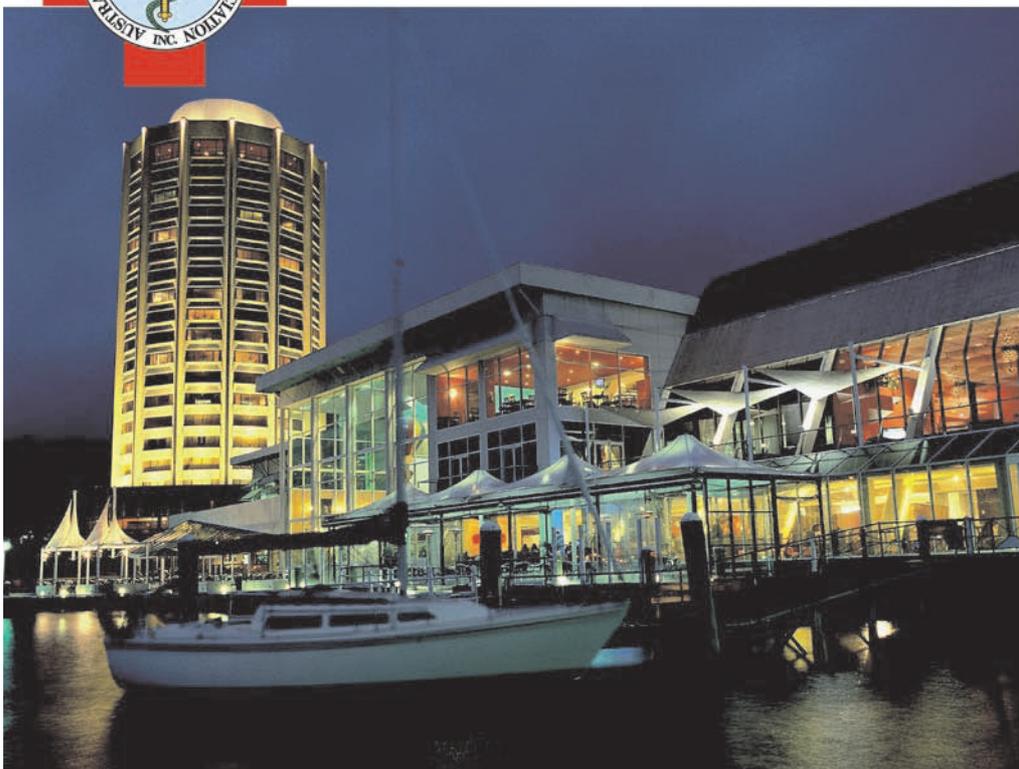
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