Syphilis

Diagnosis and management in general practice

BACKGROUND Although largely regarded as an uncommon condition, recent outbreaks of syphilis in Western nations combined with the increasing popularity of travel are likely to result in increases in rates in Australia.
OBJECTIVES To discuss the common modes of presentation and interpretation of syphilis tests, and the treatment of syphilis at various stages.
DISCUSSION Accurate interpretation of syphilis test results is essential for staging of disease and appropriate treatment. With these skills many cases of syphilis can be effectively managed in a general practice setting.

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Syphilis is one of the most historically interesting diseases to affect humans. First named after a fictitious shepherd in a poem written by the Veronese physician Girolamo Fracastoro in 1530,[1] this condition had risen to epidemic proportions in the 15th century, ravaging Europe as the great pox.[2] The beginning of the 20th century heralded a turning point in the history of syphilis. The spirochaete *Treponema pallidum,* the causative organism of syphilis, was observed and named in 1905. Following the discovery of penicillin in the 1930s, and its widespread use as a syphilis treatment after World War 2, the reported incidence of early syphilis decreased markedly in the developed world.[3] However this trend has not continued. Despite the decline in notifications since 1980,[4] changes in sexual behaviour resulting from the advancement of HIV treatment, and the accessibility of air travel, have contributed to the spread of syphilis and recent outbreaks in the Western world.

Recent studies have reported syphilis outbreaks in Europe: Manchester,[5] Brighton,[6] Stockholm,[7] Amsterdam,[8] Dublin,[9] and North America: Southern California,[10] Alabama.[11] These are largely associated with groups of men — those who have bisexual and homosexual contacts and heterosexual male prisoners.

Traditionally in Australia, syphilis has been reported more commonly in rural and remote areas via heterosexual and vertical spread amongst members of the indigenous community.[4] A recent review of syphilis surveillance in central Sydney, has shown that from April 1999 to March 2000, of the syphilis notifications received, only 12% of cases were of Aboriginal or Torres strait Islander descent, and 41% were acquired overseas. Among the same group, only 31% of cases were born in Australia.[12] The increase in syphilis infections in other developed nations coupled with the popularity of Australia as a holiday destination may lead to a rise in the number of cases in the near future.

This review aims to describe the common modes of presentation, interpretation of syphilis tests and treatment of syphilis at various stages.

Syphilis in general practice

The Australian urban general practitioner may have little practical experience with syphilis. In order to successfully diagnose syphilis, as with all sexually transmitted infections, an accurate sexual history is essential. To obtain honest and reliable information, this must be conducted in an open, nonjudgmental manner, using terms understood by both doctor and patient. An accurate history must include recent sexual contacts: timing, type (eg. casual partners, male or female, in Australia or abroad) and condom use, as well as a history of current symptoms if any.

A serological syphilis screen is a simple and cheap test for anyone presenting for sexual health check ups and STD screens. A history of sexual risk combined with clinical signs and symptoms consistent with syphilis of any stage, as discussed below, should alert the GP to the possibility. Various differential diagnoses exist for each stage of syphilis — the most common in Australia for an ulcerative genital lesion is genital herpes. For secondary syphilis the rash may be confused with pityriasis rosea, condylo-

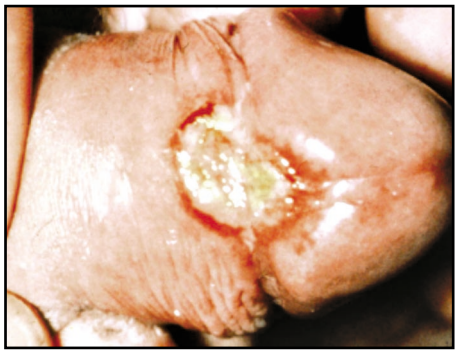

Figure 1. Primary penile chancre.
(Courtesy of the Australasian College of Sexual Health Physicians)

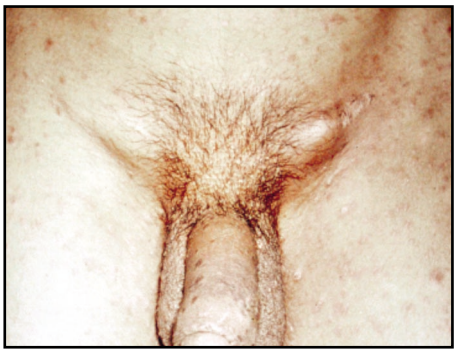

Figure 2. Rash and lymphadenopathy of secondary syphilis.
(Courtesy of the Australasian College of Sexual Health Physicians)

mata lata with genital warts and so on. Syphilis is an important infection to recognise and diagnose as it carries significant associated morbidity and mortality, yet is easily treatable.

Syphilis

The agent of venereal syphilis is the spirochaete *Treponema pallidum* subspecies *pallidum*. The infection is usually acquired by sexual contact, requiring exposure to moist mucosal or cutaneous lesions. The rate of acquisition from an infected sexual partner with early syphilis has been estimated at about 30%.[13]

Transmission of syphilis occurs from mother to child, and with safe effective treatment in pregnancy, testing for syphilis should continue to form part of a routine antenatal blood screen. Congenital syphilis will not be discussed here.

Syphilis is a systemic infection characterised by different stages, each with distinct clinical features as shown in *Table 1.*

Primary syphilis

Primary syphilis is characterised by the classical chancre, a painless ulcer which occurs at the site of inoculation and may pass unnoticed by the patient. The primary chancre is extremely infectious and will heal spontaneously after several weeks *(Figure 1).*

Secondary syphilis

The systemic symptoms of secondary syphilis reflect the dissemination of treponemes. Most patients will experience a rash. This is typically scaly, macular papular, involving the trunk and extremities, including the palms and sole *(Figure 2).* The patient at this stage, while symptomatic, is very infectious. The symptoms last for several weeks to months and resolve spontaneously, however relapse may occur in about 25% of untreated patients.

Latent syphilis

Latent syphilis is categorised into early latent syphilis or late latent syphilis. In both cases, the patient remains asymptomatic despite reactive syphilis serology. Asymptomatic infection in the first two years is known as early latent syphilis. Late latent syphilis begins two years after infection and is associated with an increasing immunity to reinfection and relapse. Latency may last years and up to two-thirds of untreated patients with latent syphilis will not progress further, remaining at this stage for life.

Tertiary syphilis

One-third of untreated patients progress to tertiary syphilis, which occurs after months to years of latency. Tertiary syphilis is rarely seen in Australia today. Believed to be associated with a decreased immunological function, it is the result of treponeme invasion of the cardiovascular system, central nervous system, skin, eyes and other organs. The symptoms of tertiary syphilis are dependant upon the system affected *(Table 1)* and result from invasion and multiplication of treponemes, the associated inflammation and host response of a delayed type hypersensitivity reaction. During both latent and tertiary syphilis sexual transmission does not occur.

Syphilis and HIV

Syphilis and other sexually transmitted diseases which cause genital ulceration, are important risk factors in the acquisition and transmission of HIV. Several studies have shown that clinical manifestations of syphilis may be altered in those with concurrent HIV infection.[14,15] These patients should be referred to a specialist sexual health clinic for management as they may require more protracted forms of treatment and follow up.

Serological tests for syphilis

In general practice, serological testing is essential for the diagnosis of all stages of syphilis. There are two types of serological tests available: treponemal and nontreponemal. Combinations of both are required for diagnosis and staging of disease *(Table 2, Figure 3).* Serological testing does not differentiate between venereal syphilis and the endemic treponematoses, such as yaws and pinta, where diagnosis is determined by history alone.

Nontreponemal tests (RPR, VDRL)

Laboratories in Australia will perform either the rapid plasma reagin (RPR) or the Venereal Disease Reference Laboratory (VDRL). These nontreponemal tests measure titres of nonspecific antibodies directed towards anticardiolipin, lecithin and cholesterol. Both tests may remain reactive after effective treatment, however a fourfold decrease in titres measures successful treatment, while an increase may indicate reinfection.

There are a number of limitations of the nontreponemal tests. Biological false positive results may occur in 1–2% of the general population, regardless of the test used.[16] The cause of such false positives is

Table 1. Stages of syphilis and associated clinical features

Early syphilis (<2 years duration)

Stage	Timing/onset	Clinical features
Primary syphilis	9–90 days (21 days average) post exposure	Primary chancre: typically a painless, rounded ,solitary ulcer with indurated base and clear exudate at site of infection — genital or extragenital Painless rubbery regional lymphadenopathy
Secondary (disseminated) syphilis	4–8 weeks after primary chancre (may coincide with primary lesion)	Headache, malaise, low grade fever, sore throat Rash (>75% of patients): non itchy, usually scaly macular papular involving trunk, palms and soles Generalised rubbery lymphadenopathy (50% of patients) Mucosal lesions (<25% of patients): painless, superficial lesions on mucous membranes– known as 'snail track ulcers' in the mouth. Condylomata lata: wart like papules typically in moist areas eg perianal region Alopecia: patchy or 'moth eaten' hair loss. Hepatitis (<10% of patients): typically mild. Other (rare) features: renal involvement eg. nephrotic syndrome, neurological involvement eg. meningitis, musculoskeletal involvement eg. arthritis
Early latent syphilis	Post–secondary syphilis	Patient is asymptomatic, has never had treatment for syphilis and has had a negative syphilis test within the past two years.

Late syphilis (>2 years duration)

Stage	Timing/onset	Clinical features
Late latent syphilis	> 2 years duration	Patient is asymptomatic and gives no history of syphilis treatment or a negative syphilis test in the past two years.
Tertiary syphilis (more specifically named after predominant system affected)		
a) gummatous disease	3–12 years post primary	Granulomatous lesions most commonly in skin and bone, which cause tissue damage and disfigurement.
b) cardiovascular syphilis	15–30 years post latent syphilis	Predominantly large vessel disease: aortitis, aortic aneurysm, aortic valve incompetence
c) neurological syphilis		
– asymptomatic	Early: <5 years post primary Late: >5 years post primary	Patient remains asymptomatic, however CSF is treponemal test positive
– meningovascular	5–12 years post primary	Features due to cerebral infarction secondary to endarteritis: eg. cranial nerve palsies, 'Argyll Robertson' pupils
– parenchymatous	15–20 years post primary	General paresis: features of progressive meningoencephalitis. eg. memory loss, personality change to confusion and disorientation. Tabes dorsalis: features of dorsal column degeneration. eg. lightening pains, paresthesia, ataxia, decrease reflexes.

Table 2. Testing, treatment and followup for syphilis*

Stage	Test				Treatment	Followup
	RPR	TPPA	FTA–abs	EIA		
Early syphilis						
Primary syphilis	±	±	±	±	Procaine penicillin 1 g IMI daily for 10 days + probenacid 500 mg tds PO for 10 days ***or*** Benzathine penicillin 1.8 g IMI stat or if allergic to penicillin Doxycycline 100 mg bd PO for 2 weeks ***or*** Tetracycline 500 mg qid PO for 2 weeks	Serological and clinical review at 6 months and 12 months, more frequently if patient follow up is uncertain If RPR was positive, expect a fourfold decline in titre by 6 months Discharge from followup after 1 year if RPR is stable HIV positive patients should be evaluated at 3 month intervals for one year and again at 2 years
Secondary syphilis	+	+	+	+		
Early latent syphilis	±	+	+	+		
Late syphilis						
Late latent syphilis	±	+	+	+	Procaine penicillin 1 g IMI daily for 15 days + probenacid 500 mg tds PO for 15 days ***or*** Benzathine penicillin 1.8 g IMI weekly for 3 doses ***or*** if allergic to penicillin Doxycycline 100 mg bd PO for 4 weeks ***or*** Tetracycline 500 mg qid PO for 4 weeks	Clinical evaluation is essential to exclude tertiary syphilis If RPR was negative prior to treatment, no follow up is required. If RPR was initially high (>1:32), expect a fourfold decline within 12–24 months If RPR titre was moderately raised, repeat at 3 monthly intervals until negative or serofast. Patients should be retreated if RPR titres increase or do not decline adequately or clinical features develop
Tertiary syphilis						If tertiary syphilis is suspected refer to a specialist.

* CDC guidelines 1998

unknown, however they have been associated with acute infections,[17] vaccinations[16] and pregnancy[18] as well as chronic injecting drug use,[19] autoimmune diseases[20] and diabetes.[21] With a biological false positive nontreponemal test, the specific treponemal tests remain unreactive.

Nontreponemal tests may also lack sensitivity in early primary and late syphilis. In primary infection they may not become positive for up to 3–5 weeks after contracting the infection.

Treponemal tests (TPPA/TPHA, FTA-Abs, EIA)

There are four tests commonly used in different combinations to detect antibodies directed specifically against *T. pallidum.* Australian labs will perform either the *T. pallidum* haemagglutination assay (TPHA) or *T. pallidum* particle agglutination assay (TPPA). The sensitivities and specificities of the two are thought to be comparable. These tests are the last to become positive and remain reactive for life.

The fluorescent treponemal antibody absorbed test (FTA-Abs) is used widely as a confirmatory test and is usually the first to become positive in early primary syphilis, at about 3–4 weeks after infection. The FTA-Abs will remain reactive for life except in some cases of very early treatment in primary syphilis.

Some labs may perform an enzyme immunoassay (EIA) test for syphilis. This may be used as a screening test in some places, and has been shown to have high sensitivity and specificity.[22]

Management

Accurate staging of infection is essential for effective management of syphilis *(Table 1).* Sexual history taking is an important tool, offering valuable information. Questions regarding recent sexual contacts, differing sexual activities, and high risk exposures such as casual male to male sex allow the clinician to assess risk of exposure, possible stage of disease and alert them to particular clinical signs and

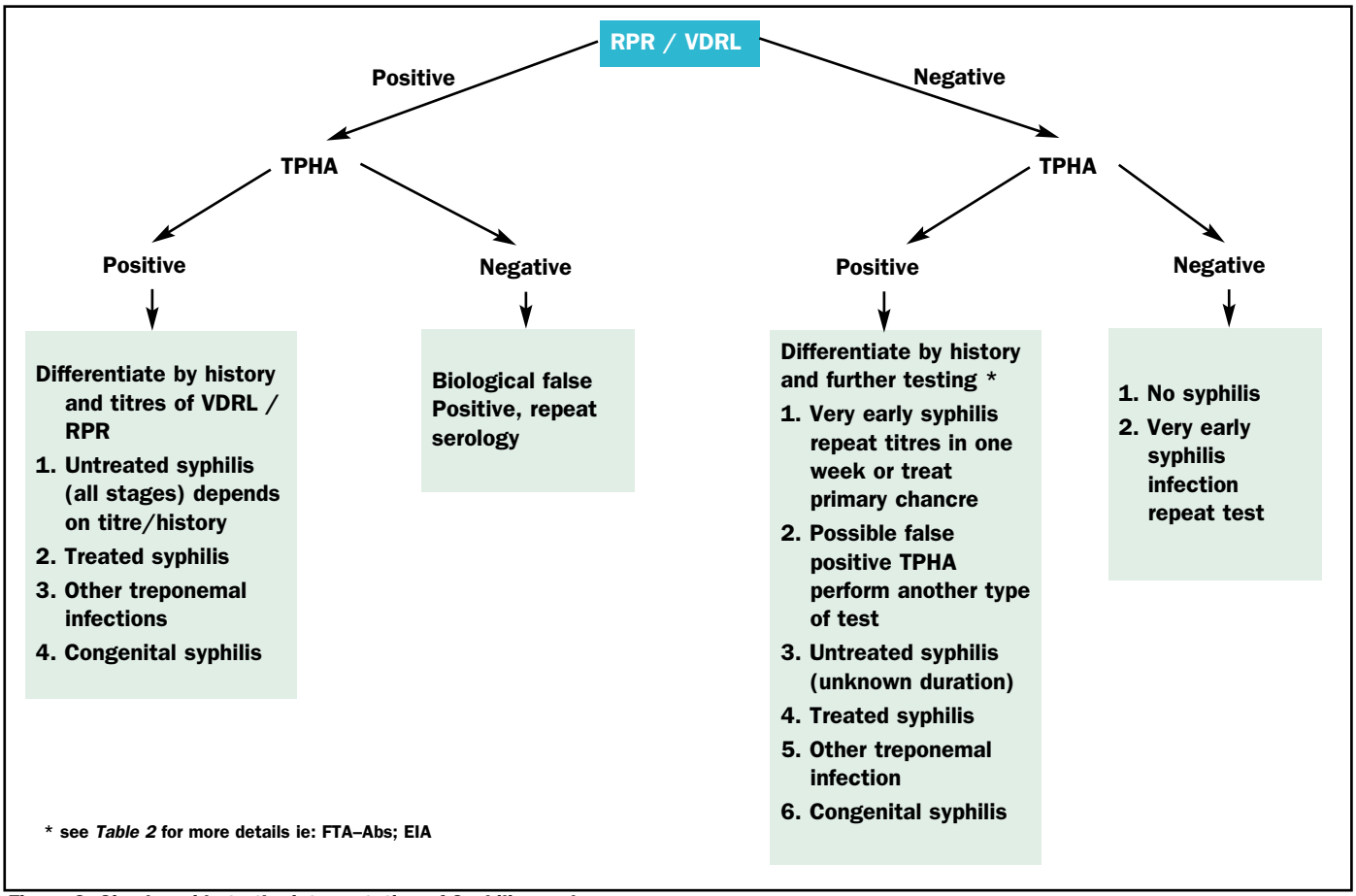

Figure 3. Simple guide to the interpretation of Syphilis serology.

symptoms. Commonly, positive syphilis serology may be found in those where syphilis was not previously suspected. These patients usually present well, with no obvious clinical features of syphilis. In this scenario, information of past history of syphilis and/or previous treatment for syphilis is invaluable.

Clinical examination may reveal signs and symptoms indicative of syphilis at various stages, however as many patients will present asymptomatically, diagnosis may rest upon serology results and history. All patients who are suspected of having syphilis should be tested for other sexually transmitted infections including HIV.

Complications of treatment

Jarisch–Herxheimer reaction

A Jarisch–Herxheimer reaction may occur in up to 50% of those with primary syphilis and up to 70% of secondary syphilis.[23] This transient flu-like reaction occurs within 24 hours after treatment, is believed to be due to the rapid destruction of treponemes and usually consists of headache, fevers and myalgia. It can be treated with simple analgesics, however it carries a risk of foetal loss when it occurs in the second or third trimester of pregnancy.

Procaine reaction

Patients treated with a procaine penicillin regimen may experience a procaine reaction, which may occur randomly, minutes after injection. The reaction manifests as extreme anxiety, a 'sense of impending doom' and, uncommonly, psychosis. Patients undergoing their first treatment should be observed for at least 30 minutes before going home.

Contact tracing

All persons exposed sexually to a patient who has syphilis of any stage are advised to have a clinical and serological evaluation. The Centres for Disease Control have defined the time periods before treatment used for identifying at risk contacts as:

- primary syphilis: three months plus duration of symptoms
- secondary syphilis: six months plus duration of treatment
- early latent syphilis: one year.

Syphilis remains uncommon in Australia, and advice should be sought from a specialist sexual health centre if there is any doubt regarding the diagnosis, staging or contact tracing of a partner in syphilis.

Conclusion

Syphilis testing should continue to form a routine practice when testing for sexually transmitted infections as the incidence of this ancient spirochete continues to escalate. Local sexual health centres can help GPs with the interpretation of syphilis serology, diagnosis, staging, management and contact tracing.

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SUMMARY OF IMPORTANT POINTS

- Recent outbreaks of syphilis have been reported in Western nations.
- A comprehensive sexual history is essential for diagnosis of syphilis and other sexually transmitted diseases.
- Syphilis presentation may vary greatly.
- Syphilis serological testing is cheap and easy to perform
- Syphilis testing should be a regular part of a sexual health check up.

REPRINT REQUESTS

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