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Syphilis, the great mimicker, is back

Background

Syphilis, which had been uncommon in Australian cities until recently, has re-emerged as a major sexually transmissible infection among men who have sex with men.

Objective

In this article we review the clinical features and management of syphilis infection, together with measures clinicians can undertake to enhance syphilis control.

Discussion

Syphilis should be considered in men who have sex with men who present with a rash or anogenital lesions. Men who have sex with men should be serologically screened for syphilis on a regular basis, including those who are HIV infected. Management of syphilis infected individuals should include adequate treatment and efforts to maximise the testing and treatment of sexual partners. Early detection and treatment of syphilis will help control the current syphilis epidemic in Australia among men who have sex with men.

■ **Syphilis is a sexually transmissible infection (STI) caused by the spirochete *Treponema pallidum*. In recent years, syphilis has re-emerged among men who have sex with men (MSM) in a number of industrialised countries, including Australia, where a substantial proportion of cases have occurred in human immunodeficiency virus (HIV) infected MSM. This has occurred on a backdrop of an increase in HIV notifications and high rates of bacterial STIs such as chlamydia and gonorrhoea among MSM in Australia.¹⁻⁴ While it is less common among heterosexuals in urban Australia, syphilis remains endemic among some remote indigenous communities and is seen in individuals who have engaged in unprotected sex while overseas.**

Clinical features

The natural history of syphilis infection is classified into stages. The clinical manifestations of these stages are shown in *Table 1*. A chancre, which is the hallmark of primary syphilis, usually appears at the site of inoculation 10–90 days (average 3 weeks) after infection.⁵ Typical chancres are shown in *Figure 1a* and *b*. Chancres may be atypical or minor, and are often overlooked by the individual.

Secondary syphilis, which is characterised by a rash, appears weeks or months after primary infection but sometimes coincides with it. Secondary syphilis represents widespread dissemination of *T. pallidum*, resulting in a spectrum of possible clinical presentations (*Table 1*). The rash of secondary syphilis (*Figure 2a–d*) is highly variable in appearance and may be mistaken for other common dermatological conditions such as psoriasis, pityriasis rosea and viral exanthems.⁶

If untreated, syphilis infection may enter a long period of latency where there are no symptoms or signs of infection. It has been estimated that if left untreated, roughly one-third of cases will



Table 1. The stages and clinical manifestations of syphilis infection

Stage	Clinical manifestations	Comments
Primary	Usually single, painless ulcer with indurated margins with or without inguinal lymphadenopathy	Sites include penis, vulva, cervix, anus, perineum and mouth (Figure 1)
Secondary	Rash – raised lesions in warm, moist regions (Figure 2)	
	Hepatitis	Rare
	Glomerulonephritis	Rare
	Ocular involvement (keratitis)	Rare
Latent syphilis	By definition, positive syphilis serology in the absence of clinical manifestations.	Classified into early and late latent infection*
Tertiary syphilis	Neurosyphilis [†]	Lumbar puncture should be considered in any individual with reactive syphilis serology who has any ophthalmic or neurological symptoms or signs
	Cardiovascular syphilis	Rare
	Gumma	Rare

* Latent infection is considered early if there is current reactive serology with documented negative serology within the previous 2 years. In the absence of such documented prior serology, latent infection should be treated as late infection

[†] Neurosyphilis can also be a manifestation of early syphilis

progress to tertiary syphilis (Table 1). Nowadays however, tertiary syphilis is rarely seen in Australia.

Syphilis infection is considered to be early if it has been acquired within 2 years, and late if acquired more than 2 years previously (Table 1). Classification into early and late infection is important as it determines the treatment regimen (Table 2).

Diagnosis

The mainstay of diagnosis of syphilis is serological testing. Serological tests for syphilis are grouped as:

- nontreponemal (or nonspecific), and
- treponemal (or specific).

Nontreponemal serology

Nontreponemal (or nonspecific) serological tests for syphilis include:

- rapid plasma reagin (RPR) test, and
- venereal disease research laboratory (VDRL) test.

The RPR and VDRL are nonspecific in that they can be reactive in the absence of syphilis. Such biological false positive results have been associated with a number of conditions, including pregnancy, autoimmune disorders and viral infections, but often the cause is unknown. False positive results should be suspected where there is an isolated reactive nontreponemal test in the absence of a reactive treponemal test, particularly where the individual is at low risk.

The titre of a nontreponemal test provides an index of the activity of syphilis infection and is used to monitor response to treatment. The RPR titre should be repeated at 3, 6, and 12 months after treatment. A fourfold drop in titre (eg. from 1:128 to 1:32) 6 months following treatment is indicative of an adequate response to treatment. (In HIV positive individuals the fourfold fall in RPR titre may take longer than 6 months to occur.) With time, the RPR titre usually becomes nonreactive, but in some cases it becomes 'serofast' or persistently reactive at a low titre for years.

Figure 1. Chancres of primary syphilis



Treponemal serology

Treponemal (or specific) serological tests for syphilis include:

- *T. pallidum* particle agglutination (TPPA)
- *T. pallidum* haemagglutination (TPHA)
- fluorescent treponemal antibody absorbed (FTA-ABS) test, and
- enzyme immunoassay (EIA).



Figure 2. Mucocutaneous lesions of secondary syphilis

A. Rash of secondary syphilis on the palms and soles



C. Condylomata lata



B. Rash of secondary syphilis



D. Alopecia as part of secondary syphilis



These tests confirm the diagnosis of syphilis, but do not indicate whether the disease is active or cured, and often remain reactive for years after effective therapy.

Syphilis serology will be positive in most but not all cases of primary syphilis. Therefore, if serology is negative in a patient with suspected primary syphilis it should be repeated. Serology is always positive in secondary syphilis where a high RPR titre is typically seen. While often seen with early syphilis, a high RPR titre in itself does not necessarily indicate early infection and can be seen with late infection.

Dark ground microscopy and PCR testing

Using dark ground microscopy, spiral shaped, motile treponemes can be visualised immediately from infectious lesions such as chancres, but such microscopy requires facilities usually only available within specialised centres. An alternative method for demonstrating the presence of *T. pallidum* from infectious lesions is to perform a swab for polymerase chain reaction (PCR) testing. At Melbourne Sexual Health Centre, PCR testing has been useful in detecting *T. pallidum* in minor anal and genital lesions where dark ground microscopy, which is relatively insensitive, has been negative.

Serological screening

Laboratories have different approaches to serological screening for syphilis – some use a treponemal test only, some a nontreponemal test only, and others use both treponemal as well as nontreponemal tests.

Sexually active MSM should be serologically screened for syphilis regularly – up to 3 monthly in those with 10 or more sex partners per year where possible – and done as part of routine STI screening of MSM.^{7,8} It is important to note that some MSM presenting to health services may not identify as homosexual or may deny a history of male-to-male sexual activity.

In HIV positive MSM, we recommend the inclusion of syphilis serology with blood tests routinely performed as part of HIV monitoring.

Syphilis screening can also be considered in heterosexual populations. While rare, except in remote Aboriginal communities and overseas contacts, there is the potential for transmission that will not be detected if not screened for. As mother-to-child transmission of syphilis can result in devastating outcomes for the newborn, women should be screened routinely for syphilis during pregnancy.



Table 2. Recommended treatments for syphilis*

Stage of infection	Treatment	Alternative treatment if penicillin allergic and not pregnant*
Primary, secondary or early latent syphilis	Benzathine penicillin 1.8 g (2.4 mU) IM as a single dose [†] OR Procaine penicillin 1.0 g IM daily for 10 days	Doxycycline 100 mg orally twice daily for 14 days [†]
Late latent or syphilis of unknown duration	Benzathine penicillin 1.8 g (2.4 mU) IM once weekly for three doses OR Procaine penicillin 1.0 g IM daily for 15 days	Doxycycline 100 mg orally twice daily for 28 days

* Management of neurosyphilis, tertiary syphilis, syphilis in HIV infected individuals, pregnant women and individuals allergic to penicillin should be managed in consultation with a specialist service

[†] Options for treating the sexual contacts of syphilis infected individuals

Treatment

Treatment of syphilis is by intramuscular injection using procaine penicillin or benzathine penicillin (*Table 2*). The disadvantage of procaine penicillin is that it must be given as a daily injection, which can be uncomfortable and inconvenient for the patient. Management of the infected individual should include an assessment of sexual risk and provision of information and support to reduce risks for re-infection or acquisition of other STIs.

Control of syphilis and management of sexual partners

Individuals with early stage syphilis are potentially infectious as the lesions of primary and secondary syphilis teem with treponemes and are highly infectious. General practitioners can play an important role in syphilis control through the early detection and treatment of syphilis, which reduces the duration of the infectious state and further transmission. Control is further enhanced through the early treatment of sexual partners.

General practitioners should emphasise to patients diagnosed with syphilis the importance of informing their sexual partners of the need for testing and possible treatment. For MSM who would prefer to contact their sexual partners anonymously, there are innovative websites that allow anonymous emailing or sending of text messages to partners (www.thedramadownunder.info/).

Immediate treatment should be offered for sexual contacts of syphilis without waiting for the results of serology if sexual contact with a person with infectious syphilis occurred less than 90 days ago, as syphilis serology may still be negative.⁹ Contacts should be offered a single dose of intramuscular benzathine penicillin, or, if benzathine penicillin is contraindicated or not readily available, oral doxycycline (*Table 2*).

Conclusion

General practitioners can play a central role in the detection, management and control of syphilis in Australia, where there is currently a syphilis epidemic among MSM.

Summary of important points

- Consider syphilis in any MSM who present with a rash or anogenital lesion.
- Screen MSM for syphilis regularly – up to 4 times a year for those who have frequent casual partners.
- In HIV infected MSM, include syphilis serology in routine blood tests done as part of HIV monitoring.
- Support syphilis infected patients to undertake all possible attempts to contact their sexual partners and consider internet based initiatives.
- Treat sexual contacts of infectious syphilis immediately, without waiting for serological results if their contact with syphilis was less than 90 days ago.

Conflict of interest: none declared.

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