Australian STI Management Guidelines for Use in Primary Care

Syphilis

Overview

- Continuing high prevalence in men who have sex with men and remote Aboriginal and Torres Strait Islander communities, and increasing prevalence in major cities.
- Recent concerning increase in prevalence in the general population, especially in women of reproductive age, so low threshold for testing is required.
- Syphilis in pregnant people has led to the re-emergence of congenital syphilis. If diagnosed during pregnancy, seek **urgent** specialist advice and ensure urgent and active recall for treatment.
- There are multiple ongoing outbreaks across Australia, especially in Aboriginal and Torres Strait Islander communities in remote areas.
- Syphilis registries can provide information and support in some states and territories.

There is currently a shortage of both strengths of Bicillin L-A (benzathine benzylpenicillin tetrahydrate) prefilled syringes for injection (600,000 units per syringe and 1.2 million units per syringe). The shortage is expected to last into 2025. During the shortage, the TGA have approved an overseas registered product, Extencilline benzathine benzylpenicillin 1.2 million unit vial (France), under section 19A of the Therapeutic Goods Act 1989.

Refer to the TGA notice and Fact Sheet for more information.

Cause

- Treponema pallidum, subspecies pallidum

Clinical presentation

Around 50% of people will have no symptoms and will only be diagnosed by screening with serological testing. The interpretation of syphilis serology is complex; previous testing results and specialist advice are often required. As syphilis can mimic many other conditions, consider syphilis testing in all patients with unexplained symptoms.

Clinically, the disease has 3 stages:

1. **Early infectious syphilis:** primary and secondary and early latent infection, ie asymptomatic infection acquired within the previous 2 years.
2. **Late latent syphilis**, i.e. asymptomatic infection acquired more than 2 years before diagnosis, or when the duration of infection is unknown.
3. **Tertiary or late symptomatic syphilis**, with neurological, cardiovascular or gummatous complications.

Symptoms
Primary syphilis • Defined by the presence of a genital, anal or oral ulcer (chancre) that occurs at the site of entry. • The ulcer is mostly (but not always) relatively painless with a well defined margin and an indurated (firm) base. • In about 30% of cases there may be multiple ulcers and other atypical presentations, so it is necessary to have a low threshold for testing in those at risk. • Ulcer may be unnoticed, especially if anal, cervical or mouth lesions. • Incubation period is 10-90 days (average 3 weeks). • Inguinal lymph nodes are usually enlarged, rubbery and non-tender. • Even if untreated, the ulcer usually spontaneously heals within a few weeks. • Primary syphilis is highly infectious to sexual contacts and to a fetus.

Secondary syphilis

• Secondary syphilis usually occurs more than 6 weeks after infection and is characterised by systemic signs and symptoms.

• The patient may present with constitutional symptoms such as fever, malaise, headache and lymphadenopathy.

• The skin is involved in over 90% of cases, most commonly with a generalised rash involving the trunk, but may just affect the palms and soles. The rash can be easily confused with drug eruptions, pityriasis rosea or guttate psoriasis.

• There may also be alopecia, mucous patches (mouth and genital) and condylomata lata (wart-like growths in the anogenital area).

• Neurological signs of visual changes, tinnitus, deafness, cranial nerve palsies or meningitis may indicate early neurosyphilis requiring intravenous therapy.

• Incubation period is 2-24 weeks (average 6 weeks).

• If untreated, symptoms slowly resolve over a period of weeks, but may recur.

• Secondary syphilis is highly infectious to sexual contacts and to a fetus.

Early latent (< 2 years) syphilis

• Early latent stage is infection in the absence of any symptoms and known to have been acquired within the previous 2 years.

• In practice, this stage means positive syphilis serology with no clinical symptoms or signs and no evidence of adequate past treatment.

• If any doubt about the length of infection, treat as late latent disease.

• Early latent syphilis is potentially highly infectious to sexual contacts and to a fetus.

Late latent (> 2 years) syphilis

• Late latent syphilis is infection for more than 2 years in the absence of any symptoms.

• After 2 years people are no longer infectious to sexual partners.

• Importantly however late latent syphilis is able to be transmitted during pregnancy to the fetus.

Tertiary syphilis

• Late symptoms and complications may develop months or years later in about one-third of cases if not treated, although this is less common in the antibiotic era.

• Complications include destructive skin lesions (gummas), cardiovascular or neurological disease.

Complications

Early neurosyphilis

• Infection involving the central nervous system (CNS) (e.g. visual changes, tinnitus, deafness, cranial nerve palsies, meningitis), require intravenous treatment.

Congenital syphilis

• Infection of fetus during pregnancy which can cause severe multi-organ disease with very high mortality and morbidity in both in-utero and neonatal periods.

See STI Atlas for images.

Diagnosis

Useful resource – ASHM Syphilis Decision Making Tool

- Diagnosis is by a combination of serology, PCR of lesions, history and clinical assessment.
- If there is a clinical suspicion of primary syphilis but serology is negative, ensure a PCR swab has been done and repeat serology after 2 weeks following presumptive treatment.
- Syphilis Point of care tests (POCT) are available in some areas, see Syphilis POC Testing for more information.

Site/Specimen	Test	Considerations
Blood	Serology: syphilis antibody	Blood specimens will be tested for an initial syphilis specific antibody using CMIA or EIA; if reactive, the laboratory will perform supplemental testing with TPPA/TPHA and RPR/VDRL
Swab of ulcer using a PCR swab	NAAT or PCR	Swab from base of any ulcer where diagnosis suspected clinically In very early infection, the NAAT test may be positive before seroconversion.

CMIA – Chemiluminescent microparticle immunoassay

EIA – Enzyme immunoassay

PCR – Polymerase chain reaction

TPPA – Treponema pallidum particle agglutination assay

TPHA – Treponema pallidum hemaglutination assay

RPR – Rapid plasma reagin

NAAT – Nucleic acid amplification test

VDRL – Venereal Disease Research Laboratory

- In patients with prior treated syphilis, antibodies detected via CMIA/EIA and TPPA tests are usually positive for life.
- The RPR is a marker for disease activity and treatment response. It

declines slowly in untreated patients but after treatment usually falls rapidly and often reverts to non-reactive.
- Re-infection is assessed based on symptoms and a significant rise in RPR titre.
- Seek specialist advice for assistance in interpreting serology results if unsure.

Clinical indicators for testing

- Refer to standard asymptomatic sexually transmitted infection (STI) check-up.
- If not already done, add on for anyone with a STI diagnosis, contact with an STI or STI symptoms.
- Pregnancy – refer to pregnant people section and ensure you are aware of any local enhanced testing guidelines, particularly for Aboriginal and Torres Strait Islander people.
- Any genital, anal and oral ulcers or lumps without a known alternative cause.
- Any unexplained rash, alopecia, fever, persistent lymphadenopathy or liver function disturbance.

Special considerations

- Positive syphilis results in a child should be urgently discussed with a specialist and child protection services.
- Include a standard asymptomatic STI check-up in anyone being tested for human immunodeficiency virus (HIV).
- Include a NAAT swab for herpes, if any anogenital or pharyngeal ulceration present.
- In remote Australia include a donovanosis PCR for any genital ulcer.

Management

There is currently a shortage of both strengths of Bicillin L-A (benzathine benzylpenicillin tetrahydrate) prefilled syringes for injection (600,000 units per syringe and 1.2 million units per syringe). The shortage is expected to last into 2024. During the shortage, the TGA have approved the importation and supply of Benzylpenicillin Benzathine (Brancaster Pharma, UK). Refer to the TGA notice and Fact Sheet for more information.

GPs should be aware their community pharmacies may not have supply of Benzylpenicillin Benzathine (Brancaster) and they may need to be proactive in ensuring access for their patients from local hospitals and publicly funded sexual health services.

- Early referral or discussion with a specialist is strongly recommended.
- Patients being treated for primary and secondary syphilis should have RPR serology repeated on the day treatment is commenced to provide an accurate baseline for monitoring treatment response.

Principle treatment option		
Situation	**Recommended**	**Alternative**
Early syphilis (primary, secondary, early latent)*	Benzathine benzylpenicillin 2.4 MU (1.8 g) IMI, Stat, given as 2 injections containing 1.2 MU (0.9 g)	Discuss with specialist
Late syphilis or syphilis of unknown duration (late latent > 2 years)	Benzathine benzylpenicillin 2.4 MU (1.8 g) IMI, given as 2 injections containing 1.2 MU (0.9 g) weekly for 3 weeks	Discuss with specialist

*If any doubt about the length of infection, treat as late latent disease.

Treatment advice

Intramuscular penicillin formulation used should be long acting, as short-acting formulations (e.g. benzylpenicillin) are ineffective. Benzathine benzylpenicillin is supplied as 1.2 MU pre-filled syringes. It is listed on the Pharmaceutical Benefits Scheme (PBS) general schedule and prescriber bag. Supply can be difficult to obtain, seek specialist advice if unable to obtain.

Special considerations

- Jarisch-Herxheimer reaction is a common reaction to treatment in patients with primary and secondary syphilis. It occurs **6-12 hours** after commencing treatment, and is an unpleasant reaction of varying severity with fever, headache, malaise, rigors and joint pains, and lasts for several hours. Symptoms are controlled with analgesics and rest. Patients should be alerted to the possibility of this reaction and reassured accordingly.

Other immediate management

- Advise no sexual contact for **7 days** after treatment is commenced, or until the course is completed and symptoms resolved, whichever is later.
- Advise no sex with partners from the last **3 months** (primary syphilis), **6 months** (secondary syphilis) or **12 months** (early latent) until the partners have been tested and treated if necessary.
- Contact tracing and presumptive treatment of partners where last contact was within 3 months.
- Provide patient with factsheet.
- Notify the state or territory health department according to local procedures.
  Where a syphilis register exists in your State, Territory or region, ensure you promptly report the required details. Where there are any concerns or ambiguity contact your local public health service for additional support.

  Syphilis Registers
  Queensland: 1800 032 238
  South Queensland: Qld-syphilis-surveillance-centre@health.qld.gov.au
  North Queensland: North-qld-syphilis-surveillance-centre@health.qld.gov.au
  South Australia Syphilis Register: 1300 232 272
  NT Syphilis Register – Darwin (08) 8922 7818; Alice Springs (08) 8951 7552

Special Treatment Situations

Situation	Recommended
Complicated syphilis	Refer those with acute neurological symptoms or suspected tertiary disease to local sexual health or infectious diseases clinic

Pregnant people	Seek urgent specialist advice. Fetal monitoring may be advised if more than 20 weeks of pregnancy. Treat as for non-pregnant according to stage. Only penicillin has been shown to be effective, so those allergic should be desensitised and treated with penicillin. Ensure partner is tested and presumptively treated. Repeat testing during pregnancy to confirm response and detect re-infection. Arrange birth and post-natal testing of mother and clinical review of baby at delivery.
Allergy to principal treatment choice	Non-penicillin regimens have less evidence than penicillin but have shown to be effective; seek specialist advice if considering alternative therapies. Early (< 2 years) syphilis: doxycycline 100 mg orally twice a day for 14 days Late (> 2 years) or unknown duration syphilis: doxycycline 100 mg orally twice a day for 28 days.
HIV co-infection	Discuss with a specialist if CD4 count < 350 cells/µL as a lumbar puncture for CSF examination may be advised.

Contact Tracing

- Notifiable condition
- Contact tracing is important to prevent re-infection and reduce transmission.
- Ongoing sexual contacts of pregnant people are the highest priority and must be presumptively treated as soon as possible to prevent re-infection during pregnancy.
- The diagnosing doctor is responsible for initiating and documenting a discussion about contact tracing.
- Trace back according to sexual history and clinical stage of infection:
    - Primary syphilis: **3 months** plus duration of symptoms or last negative test
    - Secondary syphilis: **6 months** plus duration of symptoms or last negative test
    - Early latent: **12 months** or most recent negative test
    - Late latent syphilis: Test current partner/s. If any doubt as to whether the patient has early latent or late latent syphilis, contact trace as for early latent syphilis.

- Presumptively treat all sexual contacts from the last 3 months of patients with primary or secondary syphilis regardless of serology with benzathine benzylpenicillin 2.4 MU (1.8 g) IMI, Stat.

See Australasian Contract Tracing Guideline– Syphilis for more information.

Follow Up

- To confirm patient adherence with treatment.
- To confirm contact tracing procedures have been undertaken or offer more contact tracing support.
- Repeat serology to assess response to treatment – seek specialist advice.
- Educate about condom use, contraception, HIV PrEP/PEP, safe injecting practives, consent, CST and vaccinations for HAV, HBV and HPV as indicated.

Test of cure

Review all patients clinically and with repeat RPR testing at **3 months**, then at **6 months** and (if necessary) at **12 months** after completing treatment. A 4-fold drop (e.g. 1:8 to 1:2) indicates adequate response to treatment. Seek specialist advice if RPR is rising or a 4-fold drop is not achieved by 12 months.

Consider testing for HIV and other STIs at 3-month visit, if not undertaken at first presentation, or retesting post the window period.

Auditable Outcomes

100% of patients with syphilis have had follow-up serology tests by **6 months.**

Resources

- ASHM Syphilis decision making tool
- Could It Be Syphilis? Clinical Indicator Tool
- NSW Introduction to Syphilis for Midwives and Clinicians Providing Antenatal Care Online Learning Module

Endorsement: These guidelines have been endorsed by the Blood Borne Viruses and Sexually Transmitted Infections Standing Committee (BBVSS).

Developed by: the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) ABN 48 264 545 457 | CFN 17788

Funded by: The Australian Government Department of Health