Syphilis the great mimic:
Forgotten but not gone

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CASE

A woman, aged 37 years, from regional Victoria presented to her local emergency department with a non-pruritic maculopapular rash affecting the face, neck and trunk, with sparing of the limbs, palms and soles. She had associated pharyngitis, cervical lymphadenopathy, generalised myalgias and fatigue. She had recently returned from a camping holiday in south-east Queensland, where she had sustained mosquito bites. Social history included multiple sexual partners with inconsistent use of barrier contraception, as well as recent polysubstance use with tobacco, alcohol and methamphetamine.

Respiratory multiplex polymerase chain reaction (PCR) and pregnancy tests were negative. Blood tests revealed a mild neutrophilia and transaminitis with a normal bilirubin. Considering a broad differential diagnosis, a full sexual health screen was requested, along with serologies for Epstein–Barr virus, cytomegalovirus, viral hepatitis, *Leptospira*, Ross River virus and Q fever. Empiric treatment was commenced with oral doxycycline 100 mg twice a day and, on Day 2, the patient was discharged home with clinic follow-up.

Syphilis serology subsequently revealed a reactive serum rapid plasma reagin (RPR) with a titre of 1:256, and the patient was recalled for reassessment. Although the clinical syndrome was consistent with secondary syphilis, there were additional features elicited on history that raised concern for neurosyphilis: headache, blurred vision, tinnitus and hearing loss. Upper and lower limb neurological examination was normal. Cranial nerve examination, including dilated fundoscopy, was normal except for sensorineural hearing loss confirmed on audiogram, in keeping with otosyphilis. Cerebrospinal fluid (CSF) examination showed a mild mononuclear pleiocytosis and elevated protein (Table 1).

A diagnosis of otosyphilis with likely neurosyphilis was made, with CSF sent to the state reference laboratory for further testing. Treatment was initiated with intravenous benzylpenicillin 1.8 g four-hourly and, although this was planned to continue for 15 days, after three days the patient discharged against medical advice. Oral doxycycline 100 mg twice a day was commenced on discharge with a plan to continue for 28 days.

Table 1. Summary of serum and cerebrospinal fluid results for the reviewed case

	CSF						
Serum RPR	WCC[A] (cells/μL)	Protein[B] (g/L)	FTA-ABS	TPPA	VDRL	RPR	PCR for syphilis
1:256	10	0.56	Reactive	Reactive	N/A	Non-reactive	Not detected

[A]Reference interval (RI): <5 cells/μL.

[B]RI: 0.15–0.45 g/L.

CSF, cerebrospinal fluid; FTA-ABS, fluorescent treponemal antibody absorption test; N/A, not available; PCR, polymerase chain reaction; RPR, rapid plasma reagin titre; TPPA, *Treponema pallidum* particle agglutination assay; VDRL, venereal disease research laboratory test titre; WCC, white cell count.

QUESTION 1

Why is it important to consider syphilis?

QUESTION 2

When should syphilis be tested for?

QUESTION 3

Who should be notified of a positive result?

ANSWER 1

Australia is experiencing a syphilis epidemic, with a multijurisdictional outbreak currently active across Queensland, the Northern Territory, Western Australia and South Australia.[1] Non-Indigenous men continue to account for the majority of new infections, but recent data show a disproportionate rise in notifications among women and Aboriginal and Torres Strait Islander peoples.[2–4] Victorian syphilis notification rates have increased 100-fold since 1995 (Figure 1).[4,5] Of particular concern is congenital syphilis, which, when untreated, leads to devastating outcomes, including miscarriage and stillbirth. Every new syphilis diagnosis in a woman of childbearing potential should prompt a pregnancy test with appropriate pre-test counselling.

ANSWER 2

Syphilis screening recommendations are outlined in Table 2, adapted from the Australian sexually transmissible infections (STI) management guidelines for use in primary care[6] and the Australian Society of HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) syphilis outbreak training website.[7]

ANSWER 3

Syphilis is a notifiable condition in all Australian states and territories, with mandated laboratory and clinical notification to your local public health unit.

QUESTION 4

What is the syphilis register?

QUESTION 5

What are the stages of syphilis?

ANSWER 4

Public registers in Queensland, the Northern Territory and South Australia play an active role in patient education, contact tracing and follow up. Registers assist in the interpretation of results with reference to prior testing and treatment, indicate likely duration of infection and can prevent unnecessary retreatment.

ANSWER 5

Syphilis stages are presented in Table 3.

QUESTION 6

What are the symptoms and signs of neurosyphilis?

QUESTION 7

How is neurosyphilis diagnosed?

QUESTION 8

What is the treatment and follow-up for neurosyphilis?

ANSWER 6

The presentation of early neurosyphilis might be subtle or mimic other clinical syndromes (Table 4). Assessment for neurosyphilis requires a targeted history and a complete neurological examination. Where there are new visual changes or hearing loss, dilated fundoscopic examination and audiological assessment are warranted. Late (tertiary) neurosyphilis is uncommon and described in Table 4.

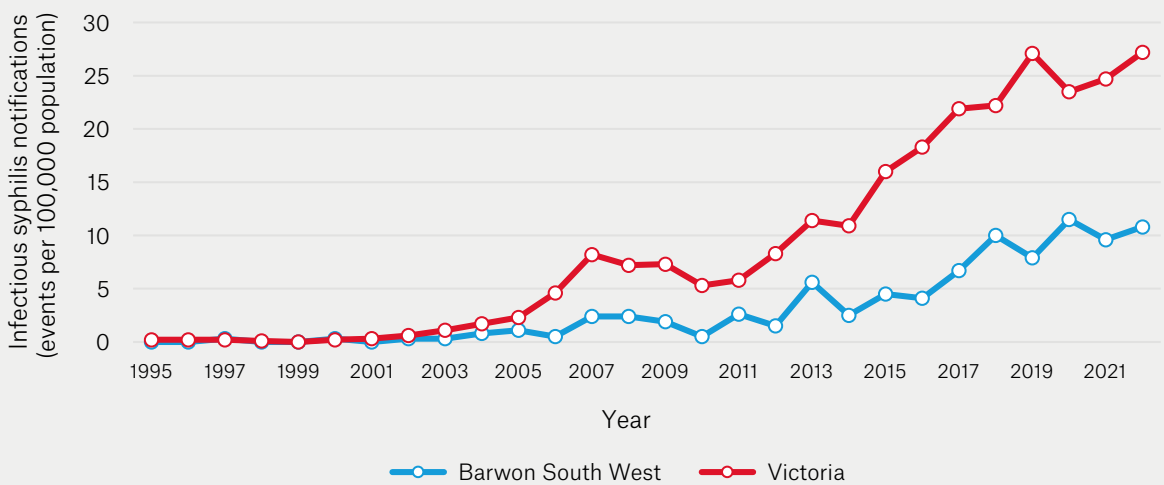

Figure 1. Infectious syphilis notifications (events per 100,000 population) from 1995 to 2022 in the Barwon South West region and Victoria. In Victoria, syphilis notification rates increased exponentially from 0.2 per 100,000 population in 1995 to 27.2 in 2022, a rise of more than 100-fold.[5] Although cases plateaued during the COVID-19 pandemic, most likely due to changes in health seeking and sexual behaviours, early data suggest that 2023 will exceed previous records.[4,5] Local data from the Barwon South West Public Health Unit show a similar trend.

ANSWER 7

Unequivocal laboratory diagnosis of neurosyphilis is challenging, and therefore a combination of symptoms, clinical signs and a panel of laboratory results is used to support the diagnosis and direct treatment. Laboratory suggestive CSF findings include a mononuclear pleiocytosis and elevated protein. Although CSF treponemal tests (fluorescent treponemal antibody absorption test and *Treponema pallidum* particle agglutination assay) are frequently reactive, they lack specificity. CSF non-treponemal tests (RPR and venereal disease research laboratory test [VDRL]) are considered diagnostic when reactive, but lack sensitivity.

ANSWER 8

Benzylpenicillin remains the mainstay of treatment for neurosyphilis, with a recommended treatment course of 15 days.[8] Although there is emerging data for the use of ceftriaxone[9,10] or doxycycline,[11] efficacy, optimal dosing and treatment duration are not well defined. Symptom review, neurological examination and repeat CSF testing are recommended at three to six months and then six-monthly thereafter until the leucocyte count is <5 g/μL and RPR/VDRL is non-reactive.[12]

Key points

- Syphilis is increasingly prevalent across Australia and should always be included as part of a routine sexual health screen.
- Neurosyphilis can occur at any stage of infection and might present subtly or mimic other clinical syndromes.
- Diagnosis is challenging, and if neurosyphilis is suspected, we recommend urgent referral to your local sexual health or infectious diseases service.

Table 2. Sexually transmissible infection screen for asymptomatic individuals and priority groups for syphilis testing[A]

Essential components of an asymptomatic STI screen as per Australian STI management guidelines for use in primary care[6]		
Any person regardless of sexual behaviours	First-pass urine (men)	PCR for *Chlamydia trachomatis* and *Neisseria gonorrhoea*
	Vaginal swab (women)	PCR for *C. trachomatis* and *N. gonorrhoea* (Note: A vaginal swab is more sensitive than first-pass urine and is the specimen of choice for women)
	Throat swab (not standard but should be considered depending on risk)	PCR for *C. trachomatis* and *N. gonorrhoea*
	Serum	Syphilis serology HIV serology HBV serology (HBsAg, anti-HBs, anti-HBc) to establish HBV status and immunise if required
Any person who engages in receptive anal intercourse	Rectal swab	PCR for *C. trachomatis* and *N. gonorrhoea*

Priority groups for syphilis testing as per ASHM:[7]

- Men who have sex with men, and their sexual contacts
- Any high-risk groups as identified during an outbreak
- People who are pregnant
- People living with HIV
- People who have previously been treated for syphilis
- People aged 15–40 years
- People with a new sexual partner/multiple partners
- At follow-up when any STI or BBV is detected
- Contacts of a person diagnosed with any STI or BBV
- People who request a sexual health screen
- Anyone during a 715 health check
- Anyone during any consultation

[A]Note that separate guidelines exist for subpopulations including men who have sex with men, sex workers, pregnant people, Aboriginal and Torres Strait Islander peoples and trans and gender-diverse people. Refer to state- or territory-based guidelines because some jurisdictions recommend additional testing beyond national guidelines.[6,7] Note also that all swabs can be self-collected.

Anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; ASHM, Australian Society of HIV, Viral Hepatitis and Sexual Health Medicine; BBV, blood-borne virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; STI, sexually transmissible infection.

Table 3. Stages of syphilis and clinical manifestations: Any of these unexplained symptoms and signs should prompt consideration of syphilis

Stage	Time after initial contact	Clinical manifestations	Infectious status	Stage at which neurosyphilis can occur
Primary	Typically 9–90 days (median 21 days) from initial contact	• Typically a painless solitary chancre: non-tender, indurated ulcer with a raised edge and clean base found at the site of contact with another infectious lesion (Note: A chancre might go unnoticed in up to 70% of individuals) • Painless regional lymphadenopathy • Occasionally primary syphilis might present as two or more painful ulcers	Infectious	Asymptomatic or symptomatic neurosyphilis can occur at any stage
Secondary	Typically 1 month to 2 years from initial contact and might progress directly from primary stage or after an early latent stage	• Mild, non-pruritic maculopapular rash, characteristically on the palms and soles; although might spare these areas and take on a different appearance (eg nodular) • Painless generalised lymphadenopathy • Oral ulceration and mucous patches • Soft, raised, wart-like lesions in moist areas (condylomata lata) • Alopecia • Periostitis • Hepatitis • Nephritis		
Latent	Early (<2 years from initial contact)	• Asymptomatic		
	Late (>2 years from initial contact)		Non-infectious	
Tertiary	Typically at least 7 years from initial contact	• Gummatous disease (painless, punched-out ulcer with little or no inflammation that might affect the skin, bone or viscera) • Cardiovascular syphilis (aortitis, aortic aneurysm, aortic valve disease or coronary ostial occlusion) • Late neurosyphilis (see Table 4)		

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Table 4. Symptoms and signs of early and late (tertiary) neurosyphilis: Any of these unexplained symptoms and signs should prompt consideration of neurosyphilis

Early neurosyphilis	**Asymptomatic neurosyphilis** No neurological symptoms or signs but diagnosed on the basis of laboratory testing	
	Acute syphilitic meningitis Symptoms and signs include: • Headache • Neck stiffness • Cranial nerve palsies such as facial droop and ophthalmoplegia • Neuropathic and radicular pain • Parasthesias • Limb weakness • Ataxia • Seizures • Psychosis • Blurred vision and other visual changes with clinical findings of uveitis, neuroretinitis or optic neuritis (ocular syphilis) • Tinnitus and hearing loss with audiometric finding of sensorineural hearing loss (otosyphilis)	
Late (tertiary) neurosyphilis	**Meningovascular neurosyphilis** Symptoms and signs include: • Stroke • Hemiparesis/hemiplegia • Dysphagia • Seizures • Tabes dorsalis Symptoms and signs include: • Argyll–Robertson pupils • Diminished deep tendon reflexes • Lower extremity pain • Sensory ataxia • Bladder and bowel incontinence	
	General paresis Symptoms and signs include: • Cognitive impairment, progressive dementia • Personality change, apathy • Psychosis • Argyll–Robertson pupils • Dysarthria • Myoclonus, hyperreflexia • Seizures	

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