



PRACTICE

CLINICAL UPDATES

Syphilis



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What you need to know

- Incidence rates of syphilis have increased substantially around the world, mostly affecting men who have sex with men and people infected with HIV
- Have a high index of suspicion for syphilis in any sexually active patient with genital lesions or rashes
- Primary syphilis classically presents as a single, painless, indurated genital ulcer (chancere), but this presentation is only 31% sensitive; lesions can be painful, multiple, and extra-genital
- Diagnosis is usually based on serology, using a combination of treponemal and non-treponemal tests. Syphilis remains sensitive to benzathine penicillin G
- Staging syphilis is important because it is the basis of management (treatment, expected treatment response, follow-up periods, and partner follow-up)
- Patients with syphilis should be screened for HIV, gonorrhoea, and chlamydia

Caused by the bacteria *Treponema pallidum*,^{1,2} syphilis is transmitted through direct (usually sexual) contact with infected mucosal lesions. Other bodily fluids are also infectious when patients are bacteraemic. With infectivity up to 10-30% per sexual contact or 60% per relationship,³ syphilis rates have risen 300% since 2000 in many Western countries.⁴⁻⁷ While most infections involve men who have sex with men, infections among people with opposite sex partners also occur.^{4,7} In addition to increasing rates, syphilis can cause early complications such as irreversible loss of vision, so awareness of the infection is important for primary care clinicians.⁸⁻¹⁰

What symptoms should alert me to this diagnosis?

While syphilis causes protean symptoms (box 1), the diagnosis should be considered in any sexually active patient with genital lesions or with rashes.¹⁶⁻¹⁸

Box 1: Symptoms of syphilis by stage of infection (see fig 1)

Primary

- Symptoms appear 10-90 days (mean 21 days) after exposure
- Main symptom is a <2 cm chancre:
 - Progresses from a macule to papule to ulcer over 7 days
 - Painless, solitary, indurated, clean base (98% specific, 31% sensitive)
 - On glans, corona, labia, fourchette, or perineum
 - A third are extragenital in men who have sex with men and in women
- Localised painless adenopathy

Secondary

- Symptoms appear 2 weeks to 6 months (mean 2-12 weeks) after exposure. Can be concurrent with, or up to 8 weeks after, chancre
- Rash—Diffuse, symmetric, on trunk (often subtle or atypical)
- Mucus lesions, condylomata lata
- Patchy alopecia (4-11%)
- Fever, headaches, generalised painless adenopathy
- Neurologic symptoms—Cranial nerve palsies (II, VIII), eye redness or pain, meningitis, changes to mental status or memory

Latent

- No symptoms
- In early latent stage (<12 months* or <24 months† after exposure) 25% of subjects relapse to secondary syphilis (90% of these in first year, 94% within 2 years)
- In late latent stage (>12* or 24† months after exposure), no relapse and not infectious

Tertiary

- 1-46 years after exposure
- Neurologic— paresis, tabes dorsalis
- Cardiovascular— aortitis
- Gummatous— necrotic granulomatous lesions

*According to US,¹¹ UK,¹² and Canadian¹³ guidelines

†According to World Health Organization¹⁴ and European¹⁵ guidelines

Primary syphilis—Patients with primary syphilis (fig 1) have a chancre at the site of inoculation—classically a solitary, painless, indurated, non-exudative ulcer (fig 2).^{17,19} While often on the glans, corona, labia, fourchette, or perineum, it may occur in the mouth (fig 3), rectum, or vagina.¹⁷ Chancres can be inconspicuous (fig 4) and resolve in 3-10 weeks, possibly explaining why 60% of patients do not recall this lesion. Chancres may be multiple, painful, or atypical due to coinfection with other bacteria or herpesvirus.²⁰ Depending on inoculum size, chancres appear 10-90 days after exposure (mean 21 days).¹⁷ Localised painless adenopathy may occur.¹⁷

Secondary syphilis—Secondary syphilis is a manifestation of bacterial dissemination and classically presents as a diffuse, symmetric, copper, maculopapular, possibly pruritic rash of any morphology except vesicular (fig 5).^{17,20,21} A rash on the palms or soles is common (11-70%, fig 6). Mucous lesions (fig 7), patchy alopecia, fever, headaches, and generalised painless adenopathy may also occur.¹⁷⁻²¹ Early neurosyphilis develops in 25-60% of people (box 1).^{9,17-22} Secondary symptoms appear 2-24 weeks after infection, concurrently with or up to eight weeks after chancres, and disappear spontaneously after several weeks with or without marking.^{17,19}

Latent syphilis—Syphilis then becomes latent, although symptoms of secondary syphilis recur in 25% of people, mostly (90%) within one year of acquiring the infection.¹⁷ Latent syphilis has early and late stages.¹⁷ Early latent disease includes the period of potential symptom relapse, classified by the WHO¹⁴ and European¹⁵ guidelines as <2 years since inoculation and as <1 year by US,¹¹ UK,¹² and Canadian¹³ guidelines. As symptom relapse indicates bacterial replication, early latent disease can be infectious. Late latent syphilis occurs >1-2 years after acquisition and is non-infectious (see fig 1).

Tertiary syphilis—Without treatment, 14-40% of people with syphilis progress to tertiary disease—irreversible damage to any organ—within 1-46 years. The damage is primarily neurologic, cardiovascular, or gummatous (necrotic granulomatous lesions pathognomonic of tertiary syphilis).^{2,17}

Which diagnostic test should be done (table 1)?

Treponema pallidum may be visualised from lesions using dark field microscopy, direct fluorescent antibody testing, or polymerase chain reaction.¹¹⁻¹⁵ Because these tests are not widely available, diagnosis predominantly relies on serology.^{17,26,27} While serologic tests and laboratory algorithms vary, testing usually begins with a screening treponemal test, such as an enzyme or chemiluminescence immunoassay (EIA or CLIA) to detect treponemal antibodies. A positive screening test should be followed by a confirmatory treponemal test, typically the *T pallidum* particle agglutination (TPPA). If both tests are positive, infection with syphilis is confirmed. Thereafter, the rapid plasma reagin (RPR) test (a quantitative non-treponemal test) should be used to measure disease activity and to track response to treatment (although 15-41% of patients remain reactive even after successful treatment).²⁸

Test timing

Screening treponemal tests (EIA or CLIA) usually become reactive first, often within two weeks of the chancre. However, patients with negative results who have syphilis-like symptoms or who report a high risk contact should be re-tested after a further two to four weeks.¹³

The RPR test may remain non-reactive for up to four weeks after the chancre, so it is often negative in primary syphilis, but it is 98-100% sensitive in secondary syphilis. However, because the RPR is a test of non-specific tissue damage, it may be positive for reasons other than syphilis.¹⁵

In the absence of treatment, a negative non-treponemal test three months after potential exposure effectively rules out a new syphilis infection.

Note that treponemal tests cannot distinguish active from treated infections and generally remain positive for life (see table 2).

Staging of syphilis

Staging of syphilis cannot be done based on laboratory results alone, and requires history and examination. Primary and secondary syphilis are symptomatic; early and late latent syphilis are generally asymptomatic. Careful examination to identify any symptoms not noticed by the patient is important and should include thorough anogenital and dermatologic inspection.²¹

The staging criteria for early latent syphilis are given in box 2. Asymptomatic patients with positive serology who do not fulfil the criteria of early latent syphilis could be staged as latent syphilis or as having syphilis of unknown duration.

Box 2: Staging criteria for early latent syphilis¹¹⁻¹⁵

Patients with early latent syphilis are asymptomatic, with one of the following:

- New positive serology with a documented negative test within previous 12* or 24† months
- ≥4-fold increase in the RPR titre relative to a previous test done within 12* or 24† months
- Unequivocal symptoms of primary or secondary syphilis within the previous 12* or 24† months
- Only one possible exposure, which occurred within previous 12* or 24† months

*According to US,¹¹ UK,¹² and Canadian¹³ guidelines

†According to World Health Organization¹⁴ and European¹⁵ guidelines

What should I do with inconclusive results?

Generally, inconclusive results arise in early infection or from waning antibody levels in late infection. The most common combinations are:

- A positive RPR with negative treponemal screening (EIA/CLIA) and confirmatory tests (TPPA) suggests the RPR result is a false positive
- A positive screen (EIA/CLIA) with negative confirmatory test (TPPA) and negative RPR is likely a false positive but could indicate early infection
- A positive screen (EIA/CLIA) with indeterminate confirmatory test (TPPA) and negative RPR could represent waning antibody levels after a previous, treated infection or a new infection.

When results are inconclusive, clinicians should inquire about previous syphilis infection and treatment, and, if early syphilis is possible, retest in two to four weeks.¹³ If results are unchanged, interpretation is based on history—consider the possibility of late untreated infection, treated infection, or non-venereal treponemal disease in adults from endemic countries in South and Central America, South-East Asia, and Africa.

What are the recommended treatment options? (box 3)

Box 3: Recommended treatments for syphilis

Primary, secondary, and early latent disease

- First line treatment
 - Benzathine penicillin G 2.4×10^6 units, single intramuscular dose*†
 - Doxycycline 100 mg, taken orally twice daily for 14 days*†
- Alternate treatments
 - Ceftriaxone 1 g, intravenous or intramuscular once daily for 10 days*
 - Procaine penicillin G 1.2×10^6 units, intramuscular once daily for 10 days†
 - Azithromycin 2 g, single oral dose†

Late latent disease

- First line treatment
 - Benzathine penicillin G 2.4×10^6 units, intramuscular dose once weekly for 3 weeks*†
 - Doxycycline 100 mg, taken orally twice daily for 28 days*†
- Alternate treatments
 - Ceftriaxone 1 g, intravenous or intramuscular once daily for 10 days*
 - Procaine penicillin G 1.2×10^6 units, intramuscular once daily for 14-21 days†

*According to US,¹¹ UK,¹² and Canadian¹³ guidelines

†According to WHO,¹⁴ UK,¹² and European¹⁵ guidelines

For primary, secondary, and early latent syphilis, in the absence of neurologic findings, first-line treatment is benzathine penicillin G (BPG) 2.4×10^6 units as a single intramuscular injection. Late latent syphilis is treated with the same dose of BPG weekly for three weeks with no more than 14 days between doses (no more than 7 days for pregnant women).¹¹⁻¹⁵ Additional BPG doses do not improve treatment outcomes for patients with early syphilis,²⁸⁻³⁰ although some guidelines suggest pregnant women with early syphilis can receive up to two doses.¹³ BPG has not been evaluated in controlled trials, but remains the first-line treatment because it is long acting (so covering the long dividing time of *T pallidum*) and because penicillin-resistant syphilis has not been documented in 60 years of the drug's use.^{28 30 31}

Non-pregnant patients who are allergic to penicillin can be given doxycycline 100 mg by mouth twice daily for two weeks for primary, secondary, and early latent syphilis, or for four weeks for late latent syphilis,¹¹⁻¹⁵ although doxycycline, compared with BPG, may yield more treatment failures (defined according to the CDC as a fourfold or higher increase in RPR titre).^{28 30 31} There is no alternative treatment to BPG for pregnant women.

Counsel patients about the possibility of Jarish-Herxheimer reactions, which start two to four hours after treatment and usually resolve within 24 hours. Symptoms include fever and systemic symptoms (such as chills, rigors, myalgias, arthralgias) with worsening rash or chancre.¹⁷ While UK guidelines¹² state prednisolone can be used for symptom management, other guidelines^{11 13-15} recommend only over-the-counter antipyretics.

What about follow-up?

Because syphilis has no test-of-cure, conversion to a non-reactive RPR is the best evidence of successful treatment.²⁸ Patients should be tested at the start of treatment and monitored at six and 12 months. No clinical data guide interpretation of RPR titres after treatment, and guidelines are based on expert opinion. See table 3 for recommendations from European, UK, US, Canadian, and WHO guidelines.¹¹⁻¹⁵

When should I consider evaluation of cerebrospinal fluid?

Indications for lumbar puncture and evaluation of cerebrospinal fluid (CSF) include neurologic symptoms or tertiary disease (table 3).¹¹⁻¹⁵ CSF evaluation can also be considered for the 10-20% of patients with earlier disease who do not achieve a fourfold decline in RPR titres by 6-12 months after treatment.¹¹⁻¹⁵

Because BPG poorly penetrates CSF,¹¹ neurosyphilis should be treated with aqueous penicillin G, 4×10^6 units intravenously every 4 hours for 10-14 days. If neurosyphilis is ruled out, optimal management is unclear.¹¹ Clinicians may monitor the RPR titre until it is low or non-reactive, or repeat the treatment for early or late latent syphilis.¹¹ Factors limiting post-treatment RPR declines in the absence of neurosyphilis include prior infection, longer duration of infection, older age, HIV co-infection, and low pre-treatment titres.^{11 12 14 15}

Referral to secondary care may be necessary for patients requiring CSF evaluation and should be considered for those with uncertain diagnoses or poor response to treatment.

Are there specific considerations for patients with HIV?

Syphilis and HIV infection often co-exist.^{32 33} Patients with syphilis should be screened for HIV and, if negative, offered pre-exposure prophylaxis.³²⁻³⁴ They should also be screened for gonorrhoea and chlamydia. HIV-positive patients have additional indications for CSF evaluation (see table 3). Otherwise, diagnosis and treatment are unchanged.^{31 35-37}

How should I manage contact tracing?

Contacts (people who have had sex with a person diagnosed with infectious (early) syphilis) within 90 days should receive treatment with one dose of BPG even if their serology results are negative; asymptomatic contacts who had sex with an infected person more than 90 days ago could defer treatment until their serology results are available, but only if follow-up is assured. Discussions about contact tracing should be non-stigmatising and sensitive to patients' concerns about confidentiality. Explain that contact tracing has important benefits for the individual concerned and their contacts. It helps to limit ongoing transmission of a serious infection and prevent re-infection. Patients need help and support to notify contacts confidentially.

How this article was created

This article was created based on a review of international guidelines, expert opinion (local public health unit, STI clinic, and infectious disease department), and through a review of Medline and CINAHL, using the search term "syphilis." We also undertook a manual review of the reference lists of identified articles.

Education into practice

- Do you consider syphilis as a differential diagnosis of genital lesions and rashes among sexually active patients?
- How would you approach a conversation about contact tracing with a young man, recently diagnosed?

How patients were involved in this article

We reviewed the contents of this material with Max Ottawa, a local "community-based organisation that focuses on maximising the health and wellness of gay, bisexual, Two-spirit, queer, and other guys who are into guys, both cis and trans."

POB holds a research chair in public health and HIV prevention from the Ontario HIV Treatment Network.

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Tables

Table 1 | Diagnostic tests for syphilis²³⁻²⁵

Stage of syphilis	Testing		
	Direct	Treponemal (CLIA or EIA)	RPR
Primary	DFM: 74-86% sensitive, 85-100% specific	75% sensitive, reactive 1-4 weeks after chancre onset	60-90% sensitive, reactive 2 weeks after chancre onset
Secondary	DFA: 73-100% sensitive, 89-100% specific PCR: 82-95% sensitive, 95-98% specific	100% sensitive	98-100% sensitive
Latent	No lesions		~25% become negative
Tertiary			

CLIA = chemiluminescence immunoassay. EIA = enzyme immunoassay. RPR = rapid plasma reagin. DFM = dark field microscopy. DFA = direct fluorescent antibody stain. PCR = polymerase chain reaction.

Table 2| Interpretation of results from diagnostic tests for syphilis

Test		RPR (non-treponemal test to monitor treatment response)	Interpretation (interpret results alongside history and clinical findings)
CLIA or EIA (screening treponemal test)	TPPA (confirmatory treponemal test)		
Negative	Not done	Not done	<ul style="list-style-type: none"> No syphilis Early seroconversion
Indeterminate	Negative or indeterminate	Non-reactive	<ul style="list-style-type: none"> Likely no syphilis Rule out early seroconversion Repeat test in 2-4 weeks
Reactive	Reactive	Reactive (dilutions may vary)	<ul style="list-style-type: none"> Syphilis - Any stage - Previously treated - Other treponemal infections
Indeterminate	Reactive	Non-reactive	<ul style="list-style-type: none"> Syphilis - Any stage except secondary
Reactive	Indeterminate	Non-reactive	<ul style="list-style-type: none"> Early seroconversion - Previously treated
Reactive	Reactive	Non-reactive	<ul style="list-style-type: none"> - Previously treated
Reactive	Indeterminate	Reactive	<ul style="list-style-type: none"> - Other treponemal infections
Reactive	Non-reactive	Reactive, indeterminate, or non-reactive	<ul style="list-style-type: none"> Usually biologic false +ve Repeat tests: if results change, re-evaluate

CLIA = chemiluminescence immunoassay. EIA = enzyme immunoassay. TPPA = *T pallidum* particle agglutination. RPR = rapid plasma reagin.

Table 3| Recommendations for assessment of treatment of syphilis

	Canada ¹³	US (CDC) ¹¹	Europe ¹⁵	UK ¹²	WHO ¹⁴
Follow-up testing schedule after start of treatment (months)	3, 6, 12	6, 12	1, 3, 6, 12	3, 6, 12	NS
Criteria for serologic cure, by drop in RPR titres	Primary syphilis: fourfold by 6 months, eightfold by 12 months, 16-fold by 24 months Secondary syphilis: eightfold by 6 months, 16-fold by 12 months Early latent: fourfold by 12 months	4-fold by 6-12 months	4-fold by 6 months	4-fold by 12 months	4-fold over 2 tests (time NS)
Indications for evaluation of cerebrospinal fluid:					
HIV negative	Neurologic symptoms, tertiary disease, treatment failure, and consider if no fourfold decline in RPR by 6-12 months				NS
HIV positive	As for HIV -ve Also consider if RPR \geq 1:32 or CD4+ $<$ 350 \times 10 ³ cells/L				NS

NS = Not specified.

Figures

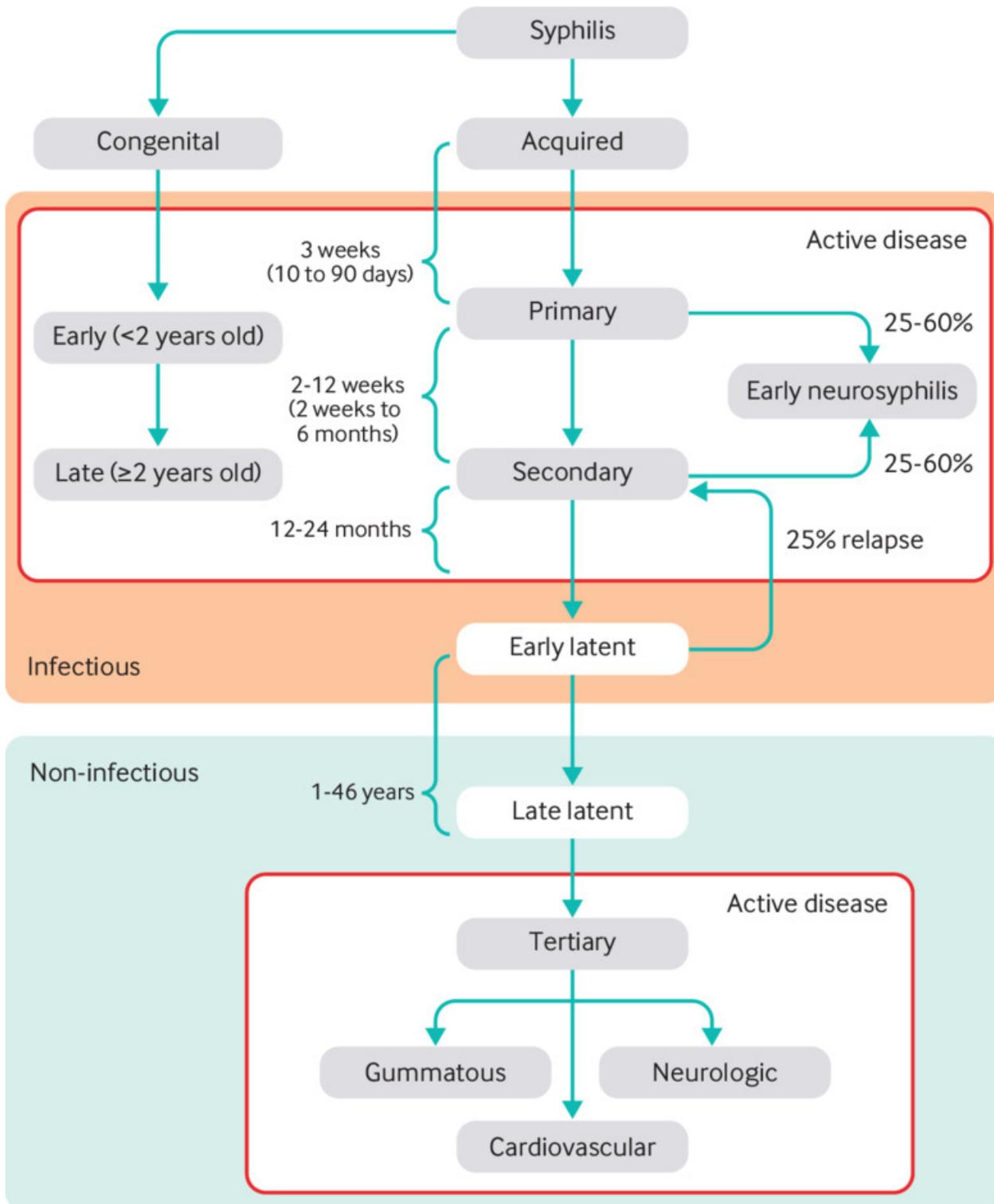


Fig 1 Stages of syphilis

BMJ: first published as 10.1136/bmj.l4159 on 28 June 2019. Downloaded from http://www.bmj.com/ on 9 August 2019 by Richard Alan Pearson. Protected by copyright.



Fig 2 Chancre (sore) on penis due to syphilis

[Image: Science Photo Library]



Fig 3 Syphilis in the mouth

[Image: CDC/Science Photo Library]



Fig 4 Inconspicuous syphilitic chancre on penis

[Image: Biophoto Associates/Science Photo Library]



Fig 5 Rash associated with secondary syphilis

[Image: Martin M Rotker/Science Photo Library]



Fig 6 Secondary syphilis on palms of hands

[Image: Southern Illinois University/Science Photo Library]



Fig 7 Condylomata lata in secondary syphilis

[Image: Science Photo Library]