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Syphilis: an update

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Clin Med 2008;8:330–3

Syphilis is caused by infection with the spirochaete bacterium *Treponema pallidum*. Transmission from one person to another is by direct contact with an infectious lesion (usually occurring during sexual contact), during pregnancy from mother to child or via infected blood products. *T. pertunue* and *T. carateum*, organisms almost identical to *T. pallidum*, cause yaws and pinta, respectively. They are indistinguishable microscopically and all three give positive results on standard serological tests for syphilis. However, yaws and pinta affect skin and bone almost exclusively and are generally found only in patients from endemic areas.

Epidemiology

Syphilis remains common worldwide. Social disruption, mobility, lack of medical services and changing sexual behaviours have contributed to epidemics. Early syphilis has re-emerged in Western Europe since the late 1990s.[1]

Most sexually acquired infectious syphilis in the UK is among men who have sex with men (MSM). New diagnoses of all sexually transmitted infections (STIs) in MSM have risen consistently for the last 10 years. This indicates a resurgence in sexual risk taking by MSM which has probably led to continuing HIV transmission within this population in the UK. In parallel with the outbreak of syphilis in MSM, clusters of early syphilis among heterosexual men and women have been reported.[2,3]

Clinical presentation

Entry of *T. pallidum* probably occurs through areas of 'microtrauma', usually in mucous membranes, and most sexual transmission of syphilis probably occurs from the genital and mucous membrane lesions of primary and secondary syphilis.

Syphilis is classified as:

- *acquired*: early (primary, secondary and early latent <2 years of infection) and late (late latent >2 years of infection)
- *congenital*: early (diagnosed in the first 2 years of life) and late (presenting after the age of 2 years).

Acquired syphilis

Primary syphilis

Primary syphilis is characterised by an ulcer (the chancre) and regional lymphadenopathy. The incubation period is 9–90 days, but the primary lesion most often appears about three weeks after transmission. The chancre is classically in the anogenital region, is single, painless and indurated with a clean base discharging clear serum. However, chancres may be multiple, painful, purulent, destructive, extragenital (most frequently oral) and may cause the syphilitic balanitis of Follman. There may also be mixed aetiology.

Secondary syphilis

Secondary syphilis is characterised by multisystem involvement within the first two years of infection, the manifestations first appearing about eight weeks after transmission. The rash of secondary syphilis is initially roseolar or macular, with more long-standing lesions becoming papular or nodular. This skin rash is typically non-irritant but may be associated with itch in dark-skinned persons. There are often condylomata lata, mucocutaneous lesions, generalised lymphadenopathy and, less commonly, patchy alopecia, anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periosteitis and glomerulonephritis.

Latent syphilis

Latent syphilis is diagnosed on serological testing with no symptoms or signs. It is early latent syphilis within the first two years of infection, beyond that it is late latent syphilis. About one-third of untreated patients will subsequently develop symptomatic late syphilis; this is categorised into neurosyphilis, cardiovascular syphilis and gummatous syphilis but which may coexist. Tertiary syphilis is a term often used synonymously with late symptomatic syphilis, but generally excludes meningovascular syphilis.

Congenital syphilis

Pregnant women with syphilis can transmit the infection to the fetus, usually transplacentally. The incidence of congenital syphilis is increasing in many developing countries. It can be prevented by antenatal screening for syphilis and treatment of pregnant women.[4]

Syphilis and HIV

Genital ulcerative diseases, including syphilis, increase the risk of acquiring and transmitting HIV. In addition, HIV infection may cause severe manifestations of early syphilis or more rapid progression to late syphilis. Most evidence suggests that initial management of syphilis in HIV and non-HIV infected persons is similar,[5,6] although in more advanced immunosuppression (ie lower CD4 count) there may be earlier neurological involvement and the need for further treatment. All patients diagnosed with syphilis must therefore be tested for HIV, and those testing positive have regular screening for syphilis.

Patients with presentations such as rashes, dementia, valvular heart disease or psychiatric problems may present to other specialties and syphilis as a cause can easily be overlooked by both patients and clinicians. General practitioners and hospital doctors should be encouraged to consider syphilis infection in the differential diagnosis to ensure earlier diagnosis and intervention. Sexual history and risk assessment are essential.

Diagnosis

The diagnosis of syphilis is made by identification of treponemes using dark-ground microscopy (DGM) or direct fluorescent antibody staining of treponemes in a histology specimen, and serological tests. Polymerase chain reaction (PCR) alone or as part of multiplex testing for *T. pallidum* in genital ulcer disease is now available in some settings.

Dark-ground microscopy

Identification of *T. pallidum* by DGM from samples taken from the genital lesions of primary and secondary syphilis allows immediate diagnosis of syphilis. It requires a specific microscope and technical skills and is therefore not feasible outside specialist services.

Polymerase chain reaction

DNA amplification by PCR provides an easy method of diagnosing early syphilis, with good sensitivity and specificity (94.7% and 98.6%, respectively).[7] It may be used on oral or other lesions where contamination with commensal treponemes is likely. In certain circumstances, PCR may be helpful in diagnosis by demonstrating *T. pallidum* in tissue samples, vitreous fluid and cerebral spinal fluid (CSF). It is, however, not a replacement for DGM in the clinic setting due to limited availability and the time taken to obtain a result.

Serological testing

Serological tests remain the main method of diagnosis for syphilis (Table 1). There are two groups of tests:

- treponemal (specific)
- non-treponemal (non-specific).

In recent years, enzyme immunoassay (EIA) tests have become established as the screening test of choice in syphilis (Table 2). A positive screening test with both positive specific and non-specific treponemal tests on the initial sample is needed to demonstrate infection.

Table 1. Serological tests for syphilis.

Treponemal tests (specific)	Treponemal enzyme immunoassay to detect IgG/IgM
	T. pallidum haemagglutination assay
	T. pallidum particle agglutination assay
	Fluorescent treponemal antibody absorbed test
	T. pallidum recombinant antigen line immunoassay
Non-treponemal tests (non-specific)	Venereal Diseases Research Laboratory carbon antigen test
	Rapid plasma reagin test

Ig = immunoglobulin.

Key Points

The incidence of infectious syphilis in the UK has remained high since the late 1990s, mainly in cities and commonly among gay men. Clusters of heterosexually acquired infections have been reported

Dark-ground microscopy (DGM) allows prompt diagnosis and treatment for infectious syphilis. Polymerase chain reaction for *Treponema pallidum* in genital ulcer is now available but should not replace DGM or serology testing

Almost all cases of congenital syphilis are easily prevented by antenatal screening for syphilis and treatment during pregnancy

Patients with symptoms or signs of possible neurosyphilis should have a cerebrospinal fluid examination

Provision of easily accessible diagnostic and treatment centres, routine antenatal syphilis screening and safe sex education remain key to effective syphilis control

KEY WORDS: diagnosis, epidemiology, syphilis, treatment

Table 2. Guide for serological findings in staging syphilis.

EIA	TPPA	RPR	FTA	Diagnosis
+	–	–	+	Early primary syphilis
+	+	–	+	Treated syphilis or untreated latent (early or late)
+	+	+	+	Untreated or treated syphilis
+	–	+	+	Primary syphilis
–	–	+	–	Biological false-positive
+	–	–	–	Likely to be false-positive. Recall patient for second sample and repeat all tests. If the patient has primary syphilis, the FTA will by now be positive. If similar results are found, likely to be false-positive. Blood should be sent to Health Protection Agency syphilis reference lab

Note:
- If all tests are negative this does not exclude early primary syphilis.
- Other treponemal infections (yaws, pinta, bejel) will give similar results.
- Negative RPR does not imply inactive disease.
- Positive treponemal tests (EIA/FTA/TPPA) in patients with a history of previously treated syphilis should not be used to make a diagnosis of syphilis reinfection. A clinical history, examination and RPR testing should be used to make this diagnosis.

EIA = enzyme immunoassay; FTA = fluorescent treponema antibody test; RPR = rapid plasma reagin test; TPPA = *Treponema pallidum* particle agglutination assay.

A second blood sample taken before treatment to confirm the results is highly recommended in case there are mislabelling and/or laboratory errors. EIA for antitreponemal immunoglobulin (Ig) M is useful if primary syphilis is suspected. IgM is detectable towards the end of the second week of infection while IgG is detectable usually in the fourth or fifth week.

All tests are usually positive in secondary and early latent syphilis (a delayed serological response may occur in secondary infection but this is rare, even in the presence of HIV), although the prozone phenomenon (a false negative response resulting from overwhelming antibody titres which interfere with the proper formation of the antigen-antibody lattice network necessary to visualise a positive flocculation test) may give false-negative results when testing undiluted serum.[8] A quantitative Venereal Disease Research Laboratory carbon antigen/ rapid plasma reagin (RPR) test should also be performed when the treponemal tests are positive as this helps stage the disease and its response to treatment.

Serological tests for syphilis require careful interpretation and should take account of patient history and clinical findings. The specific tests will usually remain positive for life after treatment, although the non-specific reaginic tests will usually revert to negative. Patients presenting with suspicious lesions or after high-risk exposure may have negative serology at presentation but require repeat screening during a three-month follow-up period.

Several rapid simple treponemal tests have been developed recently by the World Health Organization which allow increased screening coverage in settings without laboratory facilities.

Neurosyphilis

Patients with symptoms or signs of possible neurosyphilis should have a CSF examination. Most patients with neurosyphilis will have positive non-treponemal tests in CSF as well as a raised white cell count and protein.[9] A negative treponemal test on CSF excludes neurosyphilis. A positive test is highly sensitive for neurosyphilis but lacks specificity in blood-contaminated traumatic speci-

Table 3. UK guidelines for syphilis treatment 2007.

	Treatment	
	First-line	**Second-line (or alternative) treatments**
Epidemiological/incubating	Benzathine penicillin 2.4 Mu im single dose	Doxycycline 100 mg oral twice daily for 14 days *or* Azithromycin 1g oral stat
Primary, secondary, early latent	Benzathine penicillin 2.4 Mu im single dose *or* Procaine penicillin 600,000 units im daily for 10 days	Doxycycline 100 mg oral twice daily for 14 days *or* Azithromycin 1 g oral stat *or* Erythromycin 500 mg oral 4 times daily for 14 days *or* Ceftriaxone 500 mg im daily for 10 days
Late latent	Benzathine penicillin 2.4 Mu im weekly × 3 *or* Procaine penicillin 600,000 units im daily for 17 days	Doxycycline 200 mg oral twice daily for 28 days *or* Amoxicillin 2 g po tds *plus* Probenecid 500 mg qds for 28 days
Neurosyphilis	Procaine penicillin 1.8–2.4 g im daily *plus* Probenecid 500 mg oral 4 times daily for 17 days *or* Benzylpenicillin 18-24 Mu daily, given as 3–4 Mu iv every 4 hours for 17 days	Doxycycline 200 mg oral twice daily for 28 days *or* Ceftriaxone 2 g im (with lidocaine as diluent) *or* iv (with water for injections as diluent, NOT lidocaine) for 10–14 days

im = intramuscular; iv = intravenous; Mu = megaunit; qds = four times daily; tds = three times daily.

mens and where there is leakage through a damaged blood-brain barrier resulting from conditions other than syphilis.[10]

Congenital syphilis

Congenital syphilis can be diagnosed by clinical manifestations or demonstration of *T. pallidum* from suspicious lesions or body fluids.[11] Serological tests should be performed on infant's blood but not cord blood. If the infant's serum is positive on screening, treponemal IgM EIA and quantitative non-treponemal tests should be performed on paired infant and maternal blood. Serological tests detecting IgG may be positive due to passive transfer of maternal antibodies. Management and follow-up should be in close liaison with obstetric, midwifery, paediatric and genitourinary medicine physicians.

Treatment (Table 3)

Intramuscular (im) penicillin remains the treatment of choice. Standard syphilis therapy with penicillin rarely fails to cure the disease provided that serum concentrations in excess of 0.03 mg/ml are maintained for at least seven days. Benzathine penicillin is the first-line treatment in the epidemic situation that currently exists. Regimens with daily procaine penicillin for 10–21 days bring significant compliance issues which are avoided by single-dose im therapy.

Non-penicillin antibiotics that have been evaluated include doxycycline, erythromycin and azithromycin. Erythromycin is the least effective and does not penetrate well the CSF or placental barrier.[12] A recent large, prospective randomised trial suggested single-dose azithromycin is as effective in treating early syphilis as benzathine penicillin.[13] However, there are concerns regarding azithromycin treatment failure which appears to be due to intrinsic macrolide resistance in some strains of *T. pallidum*. A number of ceftriaxone regimens were effective in small studies.[14]

Patients should be warned of the Jarisch-Herxheimer reaction that in early disease causes a 'flu-like' illness and exacerbation of skin rash within 24 hours of starting treatment. In patients with cardiovascular, neurological or ophthalmic involvement it can cause serious complications, and in pregnancy has been associated with fetal distress and premature labour. Steroids started 24 hours before antitreponemal treatment are recommended.

All individuals diagnosed with syphilis should be tested for other STIs including HIV, and partners notified to reduce onward transmission. Regular follow-up serological screening for syphilis to monitor treatment response and sexual health promotion to prevent reinfection are important parts of management.

Conclusions

Syphilis is likely to remain a common disease worldwide. Awareness of its presentation, diagnosis and treatment is important for all clinicians. Syndromic management of genital ulcer diseases and rapid testing are being implemented in resource limited settings. Provision of easily accessible diagnostic and treatment centres, routine antenatal syphilis screening and safe sex education remain key to effective syphilis control.

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