CLINICAL REVIEW

Syphilis

Patrick French

University College London, Camden Primary Care Trust, London WC1E 6AUA
Patrick.French@camdenpct.nhs.uk

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Syphilis remains common worldwide, and since the late 1990s infectious early syphilis has re-emerged as an important disease in western Europe, including the United Kingdom.[1] The clinical presentation of both early and late syphilis is diverse, and patients may present to a wide range of services and clinicians, including general practitioners. This review will emphasise the clinical presentation of syphilis because once syphilis has been suspected diagnosis and curative treatment are usually simple to achieve.

SUMMARY POINTS

- Syphilis remains a common disease worldwide, and infectious syphilis has re-emerged in western Europe
- Syphilis causes considerable morbidity and facilitates HIV transmission
- The clinical presentation of syphilis is diverse, with patients presenting to a wide range of practitioners and services
- A high index of suspicion of syphilis and a low threshold for testing are essential
- Diagnosing and treating syphilis are usually straightforward

Sources and selection criteria

This review is based on Pubmed and Medline searches for syphilis (key words: syphilis, English, human) for the past five years (2000 to February 2006). I supplemented this with the literature review for the *UK National Early and Late Syphilis Guidelines* (2002).[w1-w3]

Why is syphilis important?

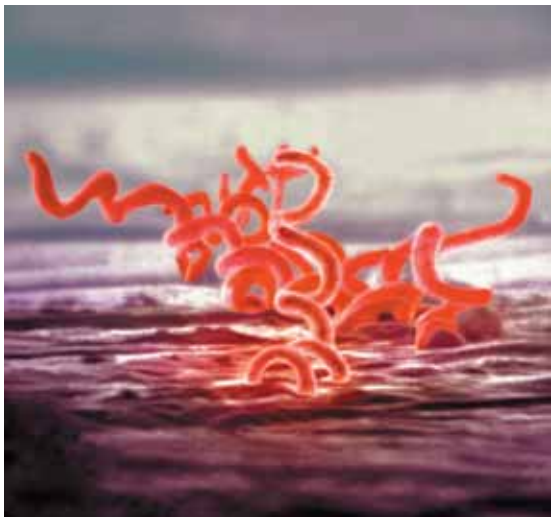
Syphilis, caused by *Treponema pallidum* (box 1, fig 1), is a common infection worldwide, with an estimated 10-12 million new infections each year.[w4] Early syphilis causes significant morbidity, and a systematic review of HIV transmission studies confirms that it is an important facilitator of HIV transmission.[3] Congenital syphilis remains a major cause of stillbirth, childhood morbidity, and mortality worldwide.[4 w4] The broad range of manifestations of late syphilis means that this diagnosis should be considered in a wide range of settings.

Who gets syphilis?

Syphilis is a sexually transmitted infection, and the more sexual partners that individuals (or other members of their sexual network) have, the more likely they are to acquire syphilis. Mobility, social disruption, and a collapse of medical services have all been recognised as factors that have contributed to syphilis epidemics: the UK during the second world war; the United States with the emergence of crack cocaine use in the late 1980s; the countries of the former Soviet Union in the mid-1990s.

Box 1| Characteristics of *Treponema pallidum*

- Coiled, motile spirochaete bacterium
- Humans are its only natural host
- Genome sequenced, very small, circular[2]
- Obligate parasite (limited metabolic capabilities)
- No in vitro culture



SCIENCE SOURCE/SPL

Fig 1 | *Treponema pallidum*

In the late 1990s syphilis re-emerged as an important infection in western Europe. Between 1984 and 1997 acquisition of syphilis in the UK was rare,[1] but since the late 1990s a sustained epidemic of syphilis has occurred in homosexual men.

In parallel to the outbreak of syphilis in homosexual men, early syphilis among heterosexual men and women in the UK has also been increasingly recognised.[5] Clusters of cases have been noted in Cambridgeshire and Walsall,[w6 w7] and syphilis outbreaks in south and east London (particularly associated with female commercial sex workers) have recently been described.[w8]

How is syphilis transmitted and classified?

It is estimated that 30-60% of sexual contacts of individuals with early syphilis will acquire syphilis themselves.[w9 w10] Entry of *T pallidum* probably occurs through areas of "microtrauma," usually in mucous

Box 2 | Stages of syphilis

- Primary syphilis
  Incubation period 2-3 weeks (range 9-90 days)
  Local infection
- Secondary syphilis
  Incubation period 6-12 weeks (range 1-6 months); generalised infection
- Early latent syphilis
  Asymptomatic syphilis of <2 years' duration
- Late latent syphilis
  Asymptomatic syphilis of ≥2 years' duration
- Late symptomatic syphilis (tertiary syphilis)
  Cardiovascular syphilis, neurosyphilis, gummatous syphilis

membranes, and most sexual transmission of syphilis probably occurs from the genital and mucous membrane lesions of primary and secondary syphilis. The classification of syphilis has not changed for over 100 years and is usually described in terms of disease stages (box 2, and more detail on bmj.com).

What is the natural course of untreated syphilis?

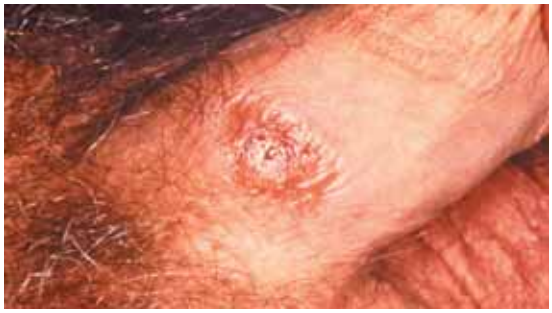
Primary syphilis

The lesion of primary syphilis occurs at the site of initial inoculation of *T pallidum*. It is usually single and painless but can be multiple and painful. It tends to begin as a macule that becomes a papule, which then ulcerates. A two to three week incubation period usually occurs between the inoculation of *T pallidum* and development of the lesion (the range of incubation period is reported as being 9-90 days). Local, non-tender lymphadenopathy is often associated with this lesion. Figure 2 shows primary syphilis lesions on the penis.

If left untreated, a lesion heals spontaneously four or five weeks later (range of healing 3-10 weeks).[w12 w13] Because the ulcers are usually painless and can occur at sites where they are not visible (perianally or in the anal canal, vagina, or cervix) or not recognised (mouth ulceration), many individuals with primary syphilis do not present to services or are not diagnosed at presentation.

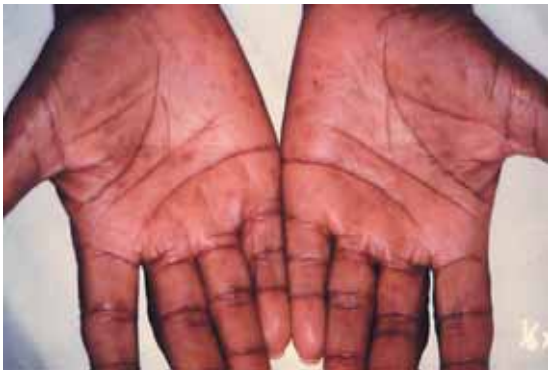
Secondary syphilis

Four to eight weeks after primary syphilis, *T pallidum* becomes a systemic infection with bacteraemia. This secondary stage of syphilis is characterised by a generalised and usually symmetrical macular papular rash,



DR G. HART, DR N J FIUMARA/CDC

Fig 2 | Primary syphilis lesion on penis



DR M F REIN/CDC

Fig 3 | Rash on palms accompanying secondary syphilis

which is often widespread and may also involve the scalp, palms (fig 3), and soles. Occasionally this rash is predominantly papular, and rarely these papules ulcerate. This can be associated with generalised lymphadenopathy and mucosal ulceration.[w11 w13] These ulcers may coalesce on the bucal mucosa, forming "snail track" ulcers, and in the genital regions (where there are opposing membranes) they can cause wart-like lesions called condylomata lata. These features are often accompanied by constitutional symptoms such as fevers and malaise.

The widespread vasculitis during secondary syphilis may lead to a broad range of syndromes such as hepatitis, iritis, nephritis, and neurological problems (early meningovascular syphilis) with headache and involvement of the cranial nerves, particularly the VIII (auditory) nerve. These complications of secondary syphilis are relatively uncommon, occurring in less than 10% of individuals.[w12]

Relapsing secondary syphilis and latent syphilis

Individuals with secondary syphilis who do not have treatment improve spontaneously over three to six weeks. About a quarter of patients have relapsing episodes of secondary syphilis, with recurrence of rash, mucosal ulceration, and fevers. These relapses are rare after one year and almost never occur after two years.[6] The infection then becomes asymptomatic (latent).

Late syphilis

About 35% of individuals with late latent syphilis will develop the late manifestations of syphilis (tertiary syphilis).[6] The three main manifestations of late syphilis are neurosyphilis, cardiovascular syphilis, and gummatous syphilis, and all these complications are currently rare outside resource poor countries.[7]

Neurosyphilis

As well as being a manifestation of secondary syphilis, meningovascular syphilis can also occur in tertiary syphilis. The incubation period is usually 5-12 years, and its symptoms are similar to those of early meningovascular syphilis.

Parenchymatous neurosyphilis is involvement of the spinal cord (predominantly dorsal columns) and brain (and occasionally both) by syphilis. The incubation period of this is usually 10-20 years. The spinal

cord syndrome is called tabes dorsalis, and the brain syndrome is called general paralysis of the insane (see extra boxes on bmj.com). Both syndromes remain important differential diagnoses for a wide range of neurological presentations, including dementia, psychiatric disease, and mobility problems.[7]

Cardiovascular syphilis

Cardiovascular syphilis usually occurs 15-30 years after primary syphilis and may occur in any large vessel. It is characterised, however, by an aortitis usually affecting the proximal aorta. It may cause aortic incompetence (which may be complicated by heart failure), coronary ostial stenosis (presenting as angina), and aortic medial necrosis causing aortic aneurysm.

Gummatous syphilis

These are granulomatous locally destructive lesions which usually occur three to 12 years after primary syphilis. They can occur in almost any tissue but most commonly present when they affect skin or bone.

The pathophysiology (particularly reasons for the variation of symptomatology between individuals) of secondary and tertiary syphilis is not clearly understood.

Congenital syphilis

Pregnant women with syphilis can transmit the infection to the fetus. Transmission is usually transplacental and is particularly likely during the first two years of infection. About a third of babies born to mothers with early syphilis are born without infection and a third with congenital syphilis; a third of pregnancies will result in miscarriage or stillbirth. Between half a million and a million cases of congenital syphilis occur each year worldwide,[4] and in some resource poor countries up to a fifth of neonatal mortality is directly attributable to syphilis.[8]

Almost all cases of congenital syphilis are easily prevented by antenatal screening for syphilis and treatment during pregnancy.[9] Even in countries where this is an unusual condition (such as the UK), an increase in cases has recently been reported,[5] and continuing vigilance remains vital.[w5] Congenital syphilis is classified as either early or late congenital syphilis depending on whether it presents before or after 2 years of age (see extra box on bmj.com). The prognosis is particularly poor if symptoms of syphilis are present in the first few weeks after birth.

HIV infection and syphilis

As syphilis is an ulcerative sexually transmitted disease, individuals with syphilis are at increased risk of acquiring and transmitting HIV. In the current syphilis outbreak in Europe, individuals who have been diagnosed with HIV are at particular risk of acquiring syphilis.[4 w14] All patients diagnosed with syphilis must therefore be tested for HIV, and those having follow-up for HIV must have regular screening for syphilis.[w14]

Box 3 | How syphilis affects patients with HIV

- Primary syphilis: larger, painful multiple ulcers[12 13]
- Secondary syphilis: genital ulcers more common and higher titres with rapid plasma reagin testing and Venereal Disease Reference Laboratory testing[12 13]
- Possibly more rapid progression to neurosyphilis[14 15]

Box 4 | Treponemal tests *v* non-treponemal tests

- Treponemal tests*
- *T pallidum* particle agglutination assay (TPPA): incubation period† 4-6 weeks
- *T pallidum* haemagglutination assay (TPHA): incubation period† 4-6 weeks
- Enzyme immunosorbant assay (EIA) IgG/IgM: incubation period 3 weeks
- Non-treponemal tests‡
- Rapid plasma reagin (RPR): incubation period 4 weeks
- Venereal Disease Reference Laboratory (VDRL): incubation period 4 weeks
- Serological response to yaws
- The serological response to yaws (caused by the non-sexually transmitted organism *T pertenue*, which rarely causes serious late disease) is identical to syphilis, so in practice most patients with suspected yaws are managed as though they have syphilis

*Usually only positive if current or past syphilis; usually positive lifelong after treatment
†Incubation period is the usual time after infection that the test becomes positive
‡Give a titre that acts as measure of disease "activity" (titre reduced with treatment, raised with reinfection); biological false positives occur with other acute and chronic infections/autoimmune disease

The clinical presentation, serological tests, and treatment response among individuals with HIV infection who also have syphilis are usually the same as among individuals without HIV infection who acquire syphilis,[10 11] but with some variation (box 3).

Some specialists recommend that a possible difference in the natural course and treatment response (particularly the possibility that neurosyphilis is a greater risk among individuals with HIV infection[16]) justifies the use of higher doses of antibiotics and longer courses for adequate treatment. But most evidence suggests that identical management of HIV positive and negative patients is reasonable, especially in early infection.[17]

What questions should be asked?

The diagnosis of syphilis (and the interpretation of syphilis serology) is often thought to be complex, but diagnosis is usually straightforward.

The history is guided by presenting symptoms. A brief sexual history may be useful to identify those individuals most at risk of syphilis; this is particularly important in asymptomatic patients. A history of negative syphilis tests (such as at sexually transmitted infection clinics or at blood donor sessions or antenatal screening)—as well any previous diagnosis and treatment for syphilis—may also be useful in evaluating patients and interpreting positive serology.

Tests for syphilis

As culture of *T pallidum* is not possible in vitro and culture in animal models is purely a research tool,

UK guidelines for syphilis treatment, 2005

Stage	First line treatment	Second line (or alternative) treatments
Primary, secondary, early latent syphilis	Benzathine penicillin 2.4 megaunits (intramuscular, single dose), or procaine penicillin 600 000 units (intramuscular, once daily for 10 days)	Doxycycline 100 mg twice daily for 14 days
Late latent syphilis	Benzathine penicillin 2.4 megaunits (intramuscular, three injections over 2 weeks: days 0, 7, 14), or procaine penicillin 900 000 units (intramuscular, daily for 17 days)	Doxycycline 200 mg twice daily for 28 days
Neurosyphilis	Procaine penicillin 2.4 units once daily (intramuscular, for 17 days) with oral probenecid 500 mg four times a day	Doxycycline 200 mg twice daily for 28 days

diagnosis testing depends on direct identification of the bacterium and serological tests.

Direct tests

Identification of *T pallidum* (seen as a motile spirochaete in a saline solution) by dark ground microscopy from samples taken from the genital lesions of primary and secondary syphilis allows the immediate diagnosis of syphilis, with a sensitivity rate of up to 97% being reported in a study from 2004.[18] But it is rarely feasible to perform this test outside specialist services. DNA amplification (polymerase chain reaction) may prove to be important in the diagnosis of early syphilis—with a sensitivity of 94.7% and a specificity of 98.6% in primary syphilis (compared with clinical diagnosis with serological confirmation) being reported in a recent study.[19]

Serology

Serological tests for syphilis remain the mainstay of diagnosis. There are two groups of tests: treponemal (or specific) and non-treponemal (or non-specific). The most important of these tests and their different and complementary characteristics are summarised in box 4.

In the past five years, enzyme immunosorbant assay (EIA) tests have become established as the screening test of first choice in syphilis.[w15] These tests can be automated and are generally reliable. A recent Health Protection Agency assessment of 10 such tests showed the sensitivity of nine of these tests to be 100% (confidence interval 98.5% to 100%) with a specificity of 100% in seven tests (97% to 100%).[w16]

Recently, several rapid simple dipstick treponemal tests have been developed. These tests have sensitivities of 85-98% compared with TPHA/TPPA testing and a specificity of 93-98%.[w17] These tests may increase the coverage of syphilis screening programmes by allowing testing in settings without laboratory facilities. All serological tests may be negative in incubating syphilis and early primary infection.

Screening for syphilis is usually done with an enzyme immunosorbant assay test. Several syphilis testing algorithms are available to allow the rational use of these tests (see algorithm on bmj.com).[20]

Patients with symptoms or signs of possible neurosyphilis should have a cerebrospinal fluid examination. Most patients with neurosyphilis will have positive non-treponemal tests in the cerebrospinal fluid examination, as well as a raised white cell count and protein.[w18]

Box 5 | National and international treatment guidelines for syphilis

World Health Organization. Guidelines for the managment of sexually transmitted infections. http://whqlibdoc.who.int/publications/2003/9241546263.pdf (last updated 2003)
Centers for Disease Control and Prevention (US guidelines). www.cdc.gov/std/treatment/ (last updated 2006)
International Union Against STIs (European). www.iusti.org/guidelines.pdf (last updated 2001)
Clinical Effectiveness Group, British Association for Sexual Health and HIV (UK guidelines). www.bashh.org (last updated 2005)

How is syphilis treated?

Penicillin was established as a highly effective treatment for syphilis long before randomised clinical trials became the norm for determining treatment efficacy. Penicillin in a variety of doses and regimens was shown to cure rapidly the lesions of early syphilis and to prevent the clinical progression of early and latent syphilis to later stages of the disease.[21]

Standard antisyphilis therapy rarely fails to cure the disease, and strains of *T pallidum* that are intrinsically resistant to penicillin have not been described. The table shows the current UK syphilis treatment recommendations, and box 5 shows online sources of the major national and international syphilis guidelines.

Newer treatments

An effective single dose oral therapy for syphilis would be a major advance in syphilis control, and a recent large prospective randomised trial suggested that 2 g oral azithromycin is as effective in treating early syphilis as benzathine penicillin.[22] This important study will probably lead to the increasing use of azithromycin for the treatment of early syphilis, but the study findings have been treated with some caution as macrolide treatment failure is well recognised and seems to be associated with intrinsic macrolide resistance in some strains of *T pallidum*.[23]

Further management and follow-up

All individuals with syphilis should be tested for other sexually transmitted infections, including HIV. The patient's partner(s) should be notified, but the role of partner notification is limited in syphilis outbreaks where many partners are not identifiable or contactable.[1 w19]

Patients who acquire syphilis are at significant risk of reinfection, so recommending regular serological screening for syphilis and providing sexual health promotion are essential parts of syphilis management.

Syphilis in the future

Syphilis is likely to remain a common disease worldwide, and some awareness of its prevention, presentation, diagnosis, and treatment is important for all clinicians. Many of the tools for effective syphilis con-

KEY AREAS OF FUTURE RESEARCH

Developing a syphilis vaccine

Establishing effectiveness of single dose oral therapy

Developing cheap, bedside diagnostic tests

ADDITIONAL EDUCATIONAL RESOURCES

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Holmes KK, Frederick Starling P, Mardh P-A, Lemon SM, Stamm WE, Piot P, et al, eds. *Sexually transmitted diseases*. New York: McGraw Hill, 1999.

Goh BT. Syphilis in adults. *Sex Transm Dis* 2005;81:448-52.

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trol (such as antenatal screening to prevent congenital syphilis) are already well established but have not been fully implemented in many parts of the world.

The likely absence of a syphilis vaccine in the foreseeable future means that syphilis control will depend largely on reducing risk taking among individuals and communities affected by syphilis and on the diagnosis and treatment of individuals with early syphilis. Comprehensive sexual health promotion programmes have been shown to reduce syphilis prevalence,[24] as have new treatment approaches such as syndromic management of genital ulcer disease.[25] Primary prevention, together with provision of easily accessible syphilis diagnostic and treatment services, will remain the cornerstone of syphilis control.

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ENDPIECE

What is research?

There are two kinds of researchers: some who are just assistants, and others whose mission is to invent. Inventions should be made in all areas, even in the humblest search for facts or the simplest experiment. Science cannot begin to exist without personal and original effort.

Henri Bergson (1859-1941) in his presidential address to the Society for Psychical Research in 1913

Submitted by Amar Bhat, senior house officer, Doncaster Royal Infirmary