Syphilis

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Abstract

Syphilis is a bacterial sexually transmitted infection caused by the spirochaete *Treponema pallidum* subspecies *pallidum*, which affects at least 11 million people worldwide every year. Case numbers in the UK now match those seen in the 1950s. Syphilis can be transmitted by oral, anal and genital sexual contact, vertically during pregnancy, and by blood transfusion. It can present with a wide range of medical symptoms and signs, and devastating sequelae can develop decades after untreated infection. Interpretation of serological tests for syphilis requires expertise to distinguish true infection from false-reactive tests. Once confirmed, treatment usually requires long-acting parenteral preparations of penicillin, followed by prolonged follow-up. For this reason, patients found to have positive syphilis serological tests should be managed by those with relevant experience.

Keywords Congenital syphilis; HIV; STI; syphilis; *Treponema pallidum*

What's new?

- Increased incidence amongst men who have sex with men, including HIV-positive men, and outbreaks in young heterosexuals in the UK
- Use of PCR for diagnosis of primary syphilis
- Simplified treatment recommendations with use of benzathine penicillin
- Characterization of high-level macrolide resistance in *T. pallidum*

Epidemiology

The incidence of syphilis, which had decreased dramatically after the Second World War with the introduction of penicillin, has increased globally in the last three decades. Developed countries have also seen a striking increase since 1997 and numbers of diagnoses in the UK are now at a level not seen since the 1950s. In 2012, nearly 3000 patients were found to have syphilis in genitourinary medicine clinics in England. Men who have sex with men (MSM) accounted for around 80% of all cases in males in England and nearly 90% in Scotland. Incidence amongst MSM is focused in urban areas such as London, Brighton and Manchester, and overlaps with epidemics of gonorrhoea, lymphogranuloma venereum, hepatitis C and *Shigella flexneri*. Most are co-infected with HIV. Outbreaks of syphilis in the UK have also been reported recently in young heterosexuals (typically less than 19 years old) in a variety of towns and rural areas. Many of those affected had social vulnerabilities. In these outbreaks, partner notification is very difficult due to high numbers of casual contacts. Congenital syphilis still occurs in the UK but is extremely rare, with the mothers of those affected typically experiencing severe socioeconomic deprivation and presenting at or near delivery. In spite of the large rise in early infectious syphilis in the UK, so far there are few reports of increases in late neurological and other sequelae. However, there are no reliable surveillance mechanisms to detect this other than in specialist genitourinary clinics and, in many people infected in the last decade, the condition may as yet be undiagnosed.

Pathology and pathogenesis

Infection with *Treponema pallidum* results in vasculitis and this process underpins the various manifestations of syphilis. A papule appears at the site of inoculation and rapidly ulcerates to form a chancre. The treponemes multiply at the site of the ulcer and spread to the local lymph nodes. Subsequently, the organisms are disseminated haematogenously and, along with immune complexes, are responsible for the manifestations of secondary syphilis. Most of the organisms are subsequently destroyed, with only small foci remaining in the spleen and lymph nodes. These remaining organisms are responsible for the persistence of serological markers of infection and after many years may lead to the manifestations of tertiary, neurological and cardiovascular syphilis. Waning of the host immune response is proposed as a likely reason for the tertiary stage, which is characterized by a granulomatous reaction to very few organisms resulting from a delayed-type hypersensitivity response.

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Clinical features

Syphilis has an extremely variable course and its clinical presentation can mimic other conditions. The natural history of syphilis is depicted in Figures 1 and 2. Current knowledge and understanding of the late manifestations of syphilis are based on several observational studies performed in the pre-antibiotic era.

Early syphilis

Primary syphilis: about 3 weeks after exposure (range: 9–90 days) patients present with a single, painless, indurated ulcer (primary chancre) 1–2 cm in diameter at the site of inoculation (Figure 3). The ulcer has a clean floor but may become secondarily infected and painful. Occasionally there may be multiple chancres. The most common sites are on the penile shaft, perineum, anal canal, labia, fourchette and cervix. Non-genital sites are the lips and nipple. The chancre is accompanied by enlargement of regional lymph nodes, which are painless and rubbery. The ulcer heals spontaneously in 3–6 weeks, leaving a scar.

Secondary syphilis: a secondary stage ensues about 6 weeks to 6 months after infection, in which an extensive, symmetrical, erythematous rash appears on the trunk and extremities (especially involving the palms and soles, Figure 4). Lesions may be macular, maculo-papular, scaly/psoriasiform or, rarely, pustular. The rash may or may not be pruritic. Mucosal patches are commonly seen on the tongue and tonsils, with classical snail-track ulcers seen on gingival margins and the buccal mucosa. In the perineum and intertriginous areas, moist flat-topped plaques (condylomata lata) appear, which are extremely infectious.

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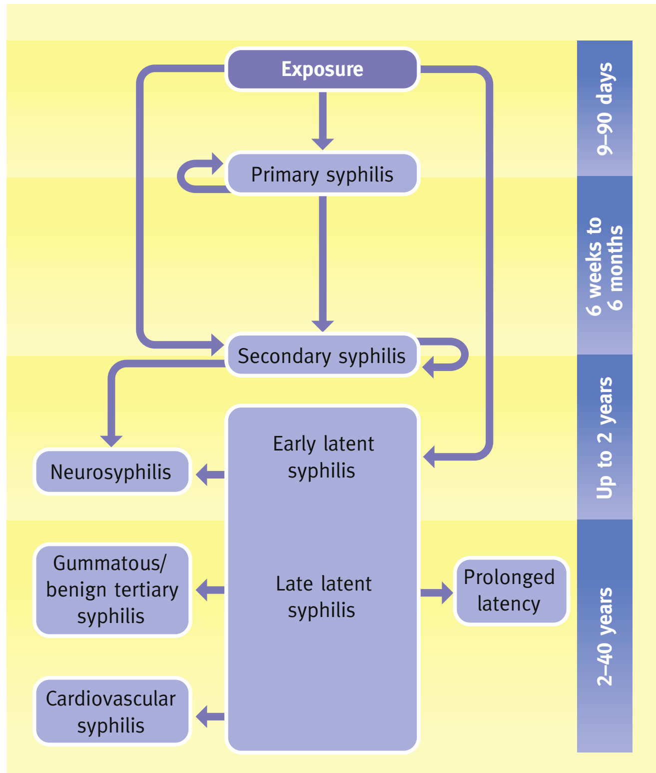

Figure 1 Natural history of syphilis.

Generalized lymphadenopathy is a common feature. The rash may be associated with systemic symptoms such as fever, headache and malaise. Patchy alopecia, anterior uveitis, optic neuritis, retinitis, hepatosplenomegaly, nephritis and asymptomatic meningitis are some of the other manifestations. This stage is also self-limiting and is followed by a latent stage. One in four patients experiences a relapse of the secondary stage up to 2 years after infection.

A significant proportion of patients may develop only the primary or the secondary stage, and some develop neither (Figure 1).

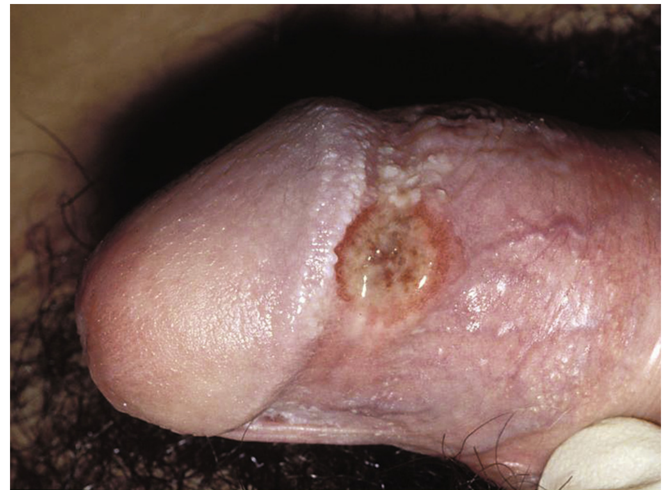

Figure 3 Primary chancre on penis.

Latent syphilis

Asymptomatic patients with positive treponemal serology but without systemic involvement are deemed to be in the latent stage. The early latent stage lasts for 2 years after infection, during which there is a higher likelihood of relapse of secondary syphilis. After 2 years patients enter a late latent stage and 60% of patients may remain asymptomatic for the rest of their lives (Figures 1 and 2).

Late syphilis

There are three types of presentations of late syphilis —benign tertiary (gummatous) syphilis, neurosyphilis and cardiovascular syphilis. These conditions are very rarely seen in the developed world nowadays, and even in the developing world the incidence is uncommon due to the widespread use of antibiotics. These conditions may occur 2—40 years after infection.

Benign tertiary syphilis is characterized by the presence of one or more gummas, which can involve any structure in the body, and presents as organomegaly (liver, spleen), a space-occupying lesion (brain) or destructive lesions (long bones, palate, nasal

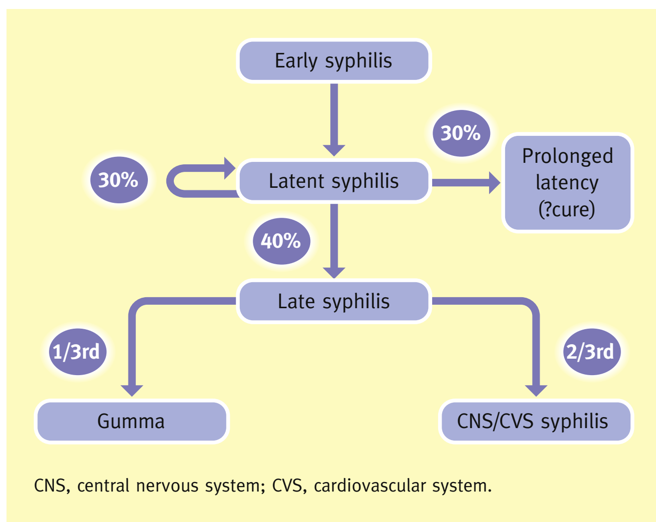

Figure 2 Natural history of syphilis in untreated individuals.

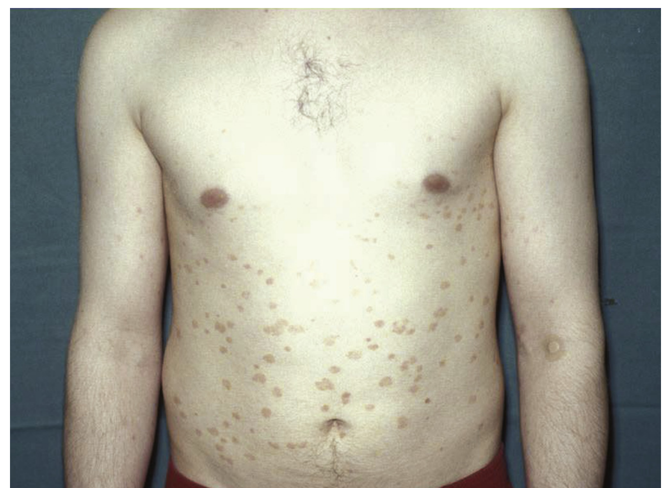

Figure 4 Secondary syphilis rash.

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