

# Primary syphilis

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**Summary:** Cases of syphilis have been increasing in the UK and it remains an important public health problem. Here, we provide an overview of syphilis, its presentation, diagnosis and management.

**Keywords:** syphilis, presentation, diagnosis, management, treatment

'Every physician should be impressed with the fact that a chancre may assume almost any conceivable morphological form, and may occur on any accessible portion of the human body except the teeth, hair and nails.'<sup>1</sup>

Stokes *et al.*<sup>1</sup> would have been disappointed had they known that, more than 60 years on, their message would go largely unheeded. Many physicians still believe that primary syphilis presents only as a 'Hunterian' chancre – a single, painless, ulcer in the genital area (Figure 1). However, primary syphilis frequently presents 'atypically'. Chancres are commonly multiple, sometimes painful and occasionally extra-genital in location.

## EPIDEMIOLOGY

The rates of infectious syphilis in UK declined after the introduction of penicillin in the 1940s. In the 1960 and 1970s, however, syphilis increased in men who have sex with men (MSM), as attitudes to homosexuality liberalized. A pronounced fall in the incidence of syphilis (particularly in MSM) occurred in the 1980s, largely because of reduction in risky sexual practices in the face of the human immunodeficiency virus (HIV) epidemic. The pendulum swung again in the late 1990s. An outbreak of syphilis, affecting mainly heterosexuals, occurred in Bristol in 1997.<sup>2</sup>

This was followed by resurgence of syphilis, mainly affecting MSM, in Manchester, UK, which began in 1999.<sup>3</sup> Similar reports soon followed from other centres in England.<sup>4–6</sup> Outbreaks also occurred in North America and Europe.<sup>7–16</sup> Subsequently, centres like Manchester have seen their syphilis outbreaks mature to endemic infection.<sup>17</sup> To date, the largest number of syphilis cases in the UK has been reported in London.<sup>18</sup>

## SYPHILIS OUTLINE

Syphilis is an important public health problem. The effects of untreated and inadequately treated infection include serious

cardiovascular and neurological disease. In addition, stillbirth and congenital syphilis may occur in pregnancies affected by syphilis. Syphilis is also an important facilitator of HIV transmission.<sup>19</sup> Although the complications of syphilis can be severe, prompt antibiotic treatment is extremely effective in preventing them. Timely diagnosis is, therefore, vital.

Syphilis is, predominantly, a sexually transmitted infection (STI), caused by the bacterium *Treponema pallidum*. Although early syphilis is an infectious continuum, it is conveniently divided into: primary, secondary and early latent stages. These were first described in detail by the Franco-American physician Ricord.<sup>20</sup>

Primary syphilis occurs as a result of direct contact of skin or mucous membranes with those of an infected person. The secondary stage results from systemic spread of treponemes, with clinical lesions classically (but not exclusively) affecting the skin, mucous membranes and lymph glands. In early latent syphilis, there are no clinical signs of infection, but treponemal serology is reactive. Late latent stage is defined as beginning two years after initial infection,<sup>21</sup> whereas in the USA, one year is the cut-off point.<sup>22</sup>

## Bacterium

*T. pallidum* subspecies *pallidum* belongs to the bacterial order Spirochaetaceae, which includes pathogenic treponemes, which cause non-venereal diseases in humans. The clinical manifestations of these infections are distinct from venereal syphilis and include yaws (*T. pallidum* subsp. *pertenue*), pinta (*T. pallidum* subsp. *carateum*) and bejel (*T. pallidum* subsp. *endemicum*). Advances in molecular biology have enabled identification of genetic differences between these treponemes.<sup>23</sup>

In the rest of this article, *T. pallidum* subsp. *pallidum* will be referred to as *T. pallidum*. *T. pallidum* is a highly motile, spiral bacterium. Its small size (0.2 µm in diameter and between 6–15 µm in length) means that dark ground microscopy (DGM) is necessary to see it. The organism has regular, tight spirals and displays rotatory, flexive and to-and-fro movements. Its body is surrounded by a cytoplasmic membrane enclosed by an outer membrane. A thin layer of peptidoglycan is sandwiched between these membranes to give added

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Figure 1 Erosive chancre of glans penis

stability. The periplasmic space contains endoflagella that facilitate the characteristic motility.<sup>24</sup>

The genome of *T. pallidum* is much smaller (1.14 MDa) than that of, for example, *Escherichia coli* (4.6 MDa) and the bacterium has surprisingly little metabolic capability. It lacks tricarboxylic acid cycle enzymes and an electron transport chain. In addition, pathways for metabolism of alternative carbon energy sources and the synthesis of nucleotides and enzyme cofactors are thought to be absent.<sup>25</sup> *T. pallidum* divides very slowly, doubling every 30–33 hours *in vivo*.<sup>26</sup> In contrast, *Neisseria gonorrhoeae* divides approximately every 60 minutes.<sup>27</sup> *T. pallidum*'s slow division time has important implications for treatment.<sup>28</sup>

*T. pallidum* obtains many essential macromolecules from its host, without which it survives for no more than a few days at most. Consequently, research into syphilis has, largely, been performed using animal models.<sup>29</sup> Inoculated rabbits develop primary and secondary lesions with similar clinical and histological features to those seen in humans.<sup>30–31</sup>

## Transmission

Most cases of syphilis are acquired through sexual transmission, by direct contact with infectious primary or secondary lesions. An individual having sexual contact with an infected partner in the previous 30 days has a 16–30% risk of acquiring syphilis.<sup>32–33</sup> However, these figures may be an underestimate of actual transmission rates.<sup>34–35</sup> *T. pallidum* enters the body via tiny breaks in the skin or intact mucous membranes. Experimental inoculation studies on humans using intradermal inoculation of *T. pallidum*, showed the 50% infectious dose to be 57 organisms.<sup>36</sup> Once inside the epithelium, *T. pallidum* reproduces locally and in draining lymph nodes. Polymorphonuclear leucocytes accumulate in the nodes, but are soon replaced by T-lymphocytes.<sup>30–37</sup> B-cells carrying surface antibody against *T. pallidum* may also be present.<sup>38</sup> *T. pallidum* is highly invasive. In rabbit experiments, spirochaetes were detectable in the bloodstream within minutes of testicular or dermal inoculation<sup>1,26</sup> and in the cerebrospinal fluid (CSF) within 18 hours of testicular inoculation.<sup>39</sup> In humans with primary and secondary syphilis, treponemes have been isolated in the CSF in 30% of cases.<sup>40</sup>

## Incubation period

The incubation period is 9–90 days, with an average of two to four weeks. Experiments in volunteers showed that larger

inocula shortened the incubation period.<sup>28</sup> The virulence of the organisms and the immune status of the recipient may also affect the incubation period.

## CLINICAL MANIFESTATIONS

### Morphology

The classical lesion of primary syphilis is a solitary, painless chancre (the latter an old French word meaning 'creeping ulcer'). The lesion evolves from a macule to a papule, which loses its covering epithelium to become an erosion. Deeper tissue loss produces an ulcer, typically of 0.5–1.5 cm in diameter. Chancres up to 10 cm diameter were reported in the pre-penicillin era.<sup>1</sup> The central surface of the chancre is clean, smooth and mucoid and produces a serous exudate. The border is typically flat, sharply demarcated and may be circled by a dull red haemorrhagic margin. The edges are flush with the surrounding skin. Chancres are indurated to the touch because of surrounding oedema and lymphocytic (mainly perivascular) infiltration. Erosions can, occasionally, become markedly hypertrophic (Figure 2).

*Chancre redux* is an unusual form of relapsing syphilis in which a primary chancre appears at or near the site of the original infection. It develops in cases of untreated or inadequately treated primary syphilis. It should not be confused with *Pseudochancre redux*, in which a tertiary syphilitic gumma develops at the site of the original chancre.

### Pain

Chancres are classically painless. However, in Chapel's series,<sup>41</sup> about one-third of patients had tender lesions, although none volunteered pain as a symptom. Pain has been reported as a prominent symptom in chancres affecting the fingers, tongue and anus.<sup>40–42</sup>

### Number

Multiple chancres are common. Chapel<sup>41</sup> reported two or more ulcers in 47% of patients with primary syphilis, whereas Duncan *et al.*<sup>43</sup> described two or more chancres in 41% of men with dark ground positive-primary syphilis. Almkvist commented that it was not unusual to see four chancres and reported one case of primary syphilis in which 20 chancres were seen.<sup>44</sup> HIV co-infection may increase the likelihood of multiple chancre formation<sup>45,46</sup> (Figures 3 and 4).



Figure 2 Hypertrophic lip erosion



Figure 3 Multiple chancres of glans

### Site

The site of the primary lesion is influenced both by the gender and sexual orientation of the patient.

### Women

In this study of 584 women with primary syphilis,<sup>47</sup> Anwyl Davies reported the sites of the lesions as cervix (44%), labia majora (31%), labia minora (8%), fourchette (6%) and urethra (3%).

### Men

Mindel *et al.*<sup>42</sup> reported chancres located on the penis in 99% of heterosexual men, compared with 64% of MSM. The commonest penile sites were the coronal sulcus (35%), the glans (29%), shaft (22%), prepuce (19%), frenulum (10%) and urethral meatus (1%) (Figure 5). Ano-rectal chancres were seen in 34% of MSM, but not in heterosexual men (Figure 6). Rarely, chancres may develop in the distal urethra.

Lesions at extra-genital sites such as the fingers, lips, tongue (Figure 7) and nipples (Figure 8) are uncommon, with reported rates between 2%<sup>42</sup> and 7%.<sup>82</sup>

### Balanitic presentation

Primary infection may present without genital ulceration, but with a superficial balanitis characterized by a flat, whitish elevations resembling bacterial colonies on agar. First described by Follmann,<sup>48</sup> the balanitis can develop before or after the appearance of the primary chancre.<sup>49</sup> Primary syphilis has



Figure 4 Kissing chancres of vulva



Figure 5 Preputial chancre + oedema

also been reported presenting with balanitis suggestive of fungal infection<sup>50</sup> (Figure 9).

### Lymph nodes

Fournier believed that satellite lymphadenopathy was the most valuable sign of syphilitic ulceration, stating that enlarged regional glands 'followed the chancre as the shadow follows the body.'<sup>1</sup> Lymphadenopathy occurs more frequently with genital lesions,<sup>41,42,51</sup> developing 7–10 days after the chancre appears. Dennie<sup>52</sup> reported that recently formed chancres were accompanied by a unilateral node enlargement, whereas the older chancres were more often accompanied by bilateral lymphadenopathy. Stokes, however, cautioned that moderate enlargement of inguinal lymph glands was absent in 30–40% of cases of primary syphilis.<sup>1</sup>

### Course untreated

Primary chancres are characteristically indolent and may persist for weeks without treatment. The chancre may be identified in about 15% of patients at the onset of the secondary stage. Chancres persisting into the secondary stage were observed more frequently in HIV-positive African-Americans.<sup>53,54</sup> Once the chancre has healed, scarring of the affected skin is very unusual.

### DIAGNOSIS

The clinical diagnosis of genital ulcer disease is unreliable, even when performed by experienced physicians.<sup>55–57</sup> Laboratory



Figure 6 Perianal chancre



Figure 7 Tongue chancre



Figure 9 Primary syphilitic balanitis

tests are the key to diagnosis. UK recommended tests for syphilis were described by Lewis and Young in 2006.<sup>58</sup> Their article was a part of a national guideline published by the British Association for Sexual Health and HIV.<sup>59</sup>

### Dark ground microscopy

Dark ground microscopy (DGM) is, currently, the only technique that allows immediate diagnosis of syphilis. It also confirms active infection, in contrast to serological tests, which may be unable to differentiate active syphilis from past infection. The ideal specimen is serous fluid uncontaminated by blood. This is obtained by cleaning the chancre with gauze soaked in normal saline solution, then gently abrading it with dry gauze and squeezing to yield serous exudate. This is placed on a glass slide and covered with a cover slip. Microscopy should be performed within 10 minutes to identify the characteristic appearance and movement of the treponemes. Anderson *et al.*<sup>60</sup> reported a sensitivity of 77.9% in DGM performed in 838 men and 26 women with primary syphilis.

In a much smaller study, Wheeler *et al.*<sup>61</sup> reported positive DGM in 30/31 cases of primary syphilis. This report also showed the limitations of DGM, which was used in only 62% of eligible cases. The reasons cited for this included the misdiagnosis of syphilis ulcers as herpetic, a broken microscope and staff lacking sufficient expertise. Indeed, lack of experience with DGM technique is widespread in the UK. An audit of senior genitourinary physicians found that 31% did not feel confident about their ability to obtain suitable specimens for DGM, and 35% doubted their ability to correctly identify the treponemes.<sup>83</sup>



Figure 8 Nipple chancre

Another limitation of DGM is its unsuitability for examining samples from oral and rectal lesions, as these sites frequently contain commensal bacteria which may be confused with *T. pallidum*. Negative DGM does not exclude syphilis. The sample may contain too few bacteria to identify, the lesion may be healing or the patient may have been treated with antibiotics. The chance of identifying treponemes is said to diminish as the size of the ulcer increases.

### Direct fluorescent antibody testing

Samples are collected as for DGM. Air-dried slides are then fixed with acetone and exposed to fluorescein-labelled anti-*T. pallidum* globulin. Direct fluorescent antibody has a sensitivity of 73–100% and a specificity of 87–100%.<sup>62</sup>

Thus, it out-performs DGM because it does not require motile bacteria and confusion with other spiral bacteria is avoided. However, the technique is not widely available and is slow in comparison with DGM.

### Nucleic acid amplification tests

Nucleic acid amplification tests, such as polymerase chain reaction (PCR) allow direct detection of *T. pallidum*. In contrast to DGM, PCR can be used on oral lesions. There are a variety of assays available; the most frequently used target is the 47-kDa protein gene, *Tpp47*. Palmer *et al.*<sup>63</sup> reported a sensitivity of 94.7% and a specificity of 98.6% compared with clinical diagnosis with serological testing.

The disadvantages of PCR include its expense, its lack of availability and delays in results.

### Serological tests

Treponemal antibody tests are the cornerstone of syphilis diagnosis. IgM antibodies are usually detectable within two to three weeks after infection, with IgG detectable about two weeks later. Although most patients who present with primary chancres have detectable IgM and IgG antibodies,<sup>64</sup> it is important to recognize that a minority will, initially, have negative serological tests. Treponemal serology does not always evolve in accordance with testing algorithms, no matter how carefully designed. Hence, it cannot be over-emphasized that clinicians should advise their testing laboratory when primary syphilis is suspected. Wherever the clinical suspicion of primary syphilis is strong, negative serology should be repeated after one to two weeks.

There are many papers detailing the characteristics of the various serological tests for syphilis. For the sake of simplicity,

Table 1 Sensitivity of serological tests in primary syphilis<sup>65</sup>

Testing method	Sensitivity (%)
TPPA	96
INNO-LIA Immunoblot Assay	94
Mercia Syphilis M EIA-IgM	88
Murex ICE EIA (IgG/IgM)	84
VDRL	70

TPPA = *T. pallidum* particle agglutination; VDRL = venereal disease research laboratory; LIA = line immuno assay; EIA = enzyme immunoassay

the performance characteristics of the tests discussed below are largely taken from a study by Manavi *et al.*<sup>65</sup> and are summarized in Table 1.

### Non-treponemal (cardiolipin) tests

#### Venereal disease research laboratory test (rapid plasma reagin test)

The non-treponemal tests or flocculation tests, use an antigen comprising cardiolipin, lecithin and cholesterol. IgG and IgM antibodies produced against lipid in the cell surface of *T. pallidum* react with the antigen. However, lipoidal antigens are also released from damaged host cells, hence the propensity for false-positive non-treponemal tests. The venereal disease research laboratory (VDRL) test is read microscopically. The rapid plasma reagin test (RPR) is a modification of the VDRL. It was designed for field-testing of finger prick specimens of blood and is read with the naked eye.<sup>66</sup>

VDRL and RPR titres are not interchangeable; RPR titres tend to be higher.

Although non-specific, the RPR/VDRL tests are the most useful for monitoring the serological response to treatment (see below).

### Treponemal tests

#### *T. pallidum* particle agglutination

For confirmation of positive non-treponemal tests, a quantitative *T. pallidum* particle agglutination (TPPA) test should be used.

#### *T. pallidum* haemagglutination

The *T. pallidum* haemagglutination (TPHA) test is less sensitive than the TPPA in primary syphilis. This may be because of inferior binding of antibody to red blood cells used in the TPHA test compared with the carbon particles used in the TPPA.<sup>67</sup>

#### Enzyme linked immunosorbent assay (EIA)

When EIAs are used, they should be tests which detect both IgM and IgG antibodies to *T. pallidum*, as these are more sensitive in primary infection.<sup>68-69</sup>

#### Immunoblot

One such test, the Murex ICE EIA (Abbott-Murex, Dartford, UK) incorporates three recombinant antigens derived from *T. pallidum*: TpN15, TpN17 and TpN47.

#### Fluorescent treponemal TA-abs

It is recommended that an additional separate EIA IgM test should be performed, to reduce the serological 'window

period'. Examples are the Mercia Syphilis M test (Microgen Products Ltd, Surrey, UK) and the INNO-LIA line immunoblot assay (Inno-genetics NV, Ghent, Belgium). The fluorescent treponemal antibody absorption (FTA-Abs) test is the most sensitive test, but it is technically difficult to perform and read. The test is not widely used.

#### Primary syphilis: differential diagnosis

- Herpes simplex virus
- Aphthous ulceration
- *Lymphogranuloma venereum*
- Penile cancer
- Tuberculosis
- Behcet's disease
- Plasma cell balanitis
- Lichen planus
- Chancere redux (see above)
- Traumatic ulceration
- Chancroid
- Granuloma inguinale
- Amoebiasis
- Reiter's syndrome
- Erythroplasia of Queyrat
- Fixed drug eruption
- Scabies
- Pseudochancere redux (see above)

### Management

Patients with primary syphilis should be screened for other STIs. An HIV test is particularly important, as management will differ in HIV co-infected patients. Sexual partners should also be screened.

### TREATMENT

Parenteral penicillin is the treatment of choice. The regimens below are taken from the UK Clinical Effectiveness Group guidelines.<sup>21</sup> These differ somewhat from European<sup>70</sup> and American<sup>22</sup> guidelines.

#### Recommended regimens

- (1) Benzathine penicillin G 2.4 MU i.m single dose
- (2) Procaine penicillin G 600 mg (600 000 units) i.m o.d. × 10 days

#### Alternative regimens

These may be required for those with penicillin allergy or refusing parenteral treatment.

- (1) Doxycycline 100 mg p.o b.d. × 14 days;
- (2) Azithromycin 2 g p.o single dose, or azithromycin 500 mg o.d. × 10 days;
- (3) Erythromycin 500 mg p.o q.i.d × 14 days;
- (4) Ceftriaxone 500 mg i.m o.d. × 10 days (if no anaphylaxis to penicillin);
- (5) Amoxicillin 500 mg p.o q.i.d + probenecid 500 mg q.i.d × 14 days.

#### Pregnancy

- First and second trimesters: benzathine penicillin G 2.4 MU i.m, single dose;
- third trimester: benzathine penicillin G 2.4 MU i.m, repeated after one week, or procaine penicillin G 750 mg i.m o.d. × 10 days.

Azithromycin should be used with caution, as azalide resistance has been reported in the USA and Ireland.<sup>71</sup>

When erythromycin or azithromycin are used in pregnancy, neonates should be evaluated for evidence of congenital

syphilis and treated with penicillin. Doxycycline is contraindicated in pregnancy. HIV-positive patients should be treated as above.

### Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction (JHR) is an influenza-like condition usually occurring 6–8 h after antibiotic treatment. It is seen in about 50% of cases of primary syphilis treated with penicillin G<sup>72</sup> and usually resolves within 12–24 hours.

Symptoms include fever, rigors, malaise, headache, sore throat, myalgia and tachycardia. It is thought to be mediated by the release of circulatory cytokines.<sup>73</sup> A large study reported more frequent JHR in patients treated with penicillin, compared with those who took erythromycin or tetracycline.<sup>60</sup>

### When does infectivity end?

A small number of studies have investigated the time taken for *T. pallidum* to disappear from chancres following treatment. Tucker and Robinson<sup>74</sup> administered a single injection of benzyl penicillin G in doses from 0.038–87.0 mg/kg. Using serial DGM, they found that most chancres became *T. pallidum*-negative between 9–48 hours. In another small study, a single 30 mg dose of benzyl penicillin G resulted in negative DGM in a mean time of 9.6 hours.<sup>75</sup>

### Follow up

Patients should attend for clinical review and repeat RPR/VDRL testing after one week. Although there is no serological test of cure for syphilis, experience has shown that a four-fold drop in the RPR/VDRL titre (e.g. from 1:16 to 1:4) equates with cure. Serology is repeated at months 1, 2, 3, 6 and 12. Titres should fall by a minimum of four-fold by 3–6 months and eight-fold by 6–12 months.<sup>76</sup>

A total of 15–25% of patients treated for primary syphilis will revert to a negative serum RPR/VDRL after 2–3 years.<sup>77</sup>

Patients can be discharged after one year of follow up, although those with HIV infection should be followed up for life.

### Management of primary syphilis in HIV co-infected patients

There have been a number of case reports describing neurosyphilitic complications in HIV-positive patients after standard treatment for early syphilis.<sup>78–80</sup>

Marra *et al.*<sup>81</sup> found that in HIV-positive patients, a pre-treatment serum RPR >1:16 or a CD4 lymphocyte count <350/ $\mu$ L increased the odds of asymptomatic neurosyphilis diagnosed by lumbar puncture (LP) by 5.98 and 3.10 fold, respectively. These increased odds were cumulative.<sup>81</sup>

The authors recommended that when benzathine penicillin G was used to treat syphilis, LP should be considered either before, or 6–12 months after treatment, as indicated by the pre-treatment serum RPR titre and/or CD4 lymphocyte count. Patients found to have CSF indices compatible with asymptomatic neurosyphilis should then be treated with an appropriate penicillin regimen. There are no longitudinal data on the effectiveness of a selective lumbar puncture policy in co-infected patients. Consequently, few patients with primary syphilis and a normal

neurological examination are likely, at this time, to undergo LP as part of their routine management. However, clinicians keenly await the results of studies in progress to determine the resolution of CSF abnormalities after treatment of early syphilis.

### CONCLUSION

Syphilis is, once more, endemic in centres in the developed world. Although affecting mostly MSM, heterosexual men and women are not immune to infection. All health professionals, not just those specializing in STIs, should be aware that primary syphilis may present to them and may be atypical in morphology. The complications of syphilis can be serious and even life-threatening, but syphilis is simple to treat provided a prompt diagnosis is made.

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