

EDUCATIONAL REVIEW ARTICLE

The Re-emergence of Syphilis in Scotland

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Learning Points

- Syphilis has re-emerged in our population in recent years, especially in men who have sex with men (MSM).
- Many cases present to specialties out-with genitourinary medicine and go unrecognised – a high index of suspicion is needed.
- It is important to know the HIV status of a person diagnosed with syphilis as this helps guide the treatment plan.
- The treatments of choice are either Procaine penicillin or Benzathine penicillin.
- It is important that anyone diagnosed with syphilis is also screened for other Sexually Transmitted Infections (STIs) and partner notification is performed.

Syphilis has re-emerged in industrialised countries in recent years including the United Kingdom (UK) and Scotland.¹ Scottish clinicians will therefore, be seeing unrecognised cases of syphilis within clinical practice. This review aims to provide an update on the recognition, diagnosis and management of syphilis for general physicians. Syphilis is known as the "great imitator" and therefore can present to any medical or surgical specialty or to primary care in a variety of ways.

What is Syphilis?

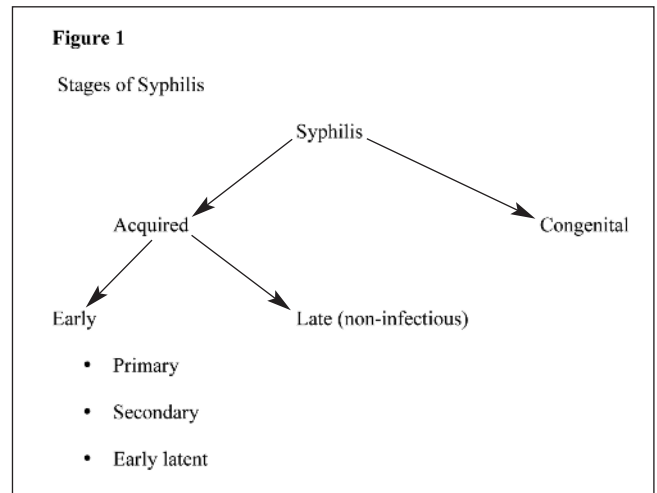
Syphilis is a systemic infection caused by the spirochaete *Treponema pallidum* subspecies *pallidum*.² Different subspecies of *Treponema pallidum* can also cause conditions known as yaws, bejel and pinta which are indistinguishable in laboratory testing. These conditions are endemic in certain parts of the world and the clinical history and nationality of the patient can help distinguish between one of these and syphilis.

How is it Acquired?

Syphilis is transmitted by close mucosal contact, including oral, anal and vaginal sex. Oral sex was the sole route of transmission implicated in 59% of cases reported in Scotland in 2006.³ Syphilis can also cross the placenta to cause congenital syphilis, and can be transmitted by blood transfusion.

What are the Different Stages of Syphilis?

Syphilis can be classified into acquired or congenital. Figure 1 outlines the various stages of acquired syphilis and the further subdivisions.



The **primary stage** may present with a chancre, an ulcer at the site of inoculation. Often this is painless and patients may not notice or report this lesion especially if this is in the mouth, so a high index of clinical suspicion is needed. However, ulcers can be multiple and painful and easily confused with genital herpes. They heal spontaneously after a few weeks. Serology may be negative at this stage and should be repeated four weeks later if syphilis is suspected.

Secondary syphilis presents between six weeks and six months later, and may relapse and remit beyond this. Some symptoms and signs of secondary syphilis are shown in Table I.

Table I Signs and Symptoms of Secondary Syphilis

Fever	Meningismus
Headache	Mucous patches
Rash – typically maculopapular	Condylomata lata
Weight loss	Neurological (deafness / optic neuritis)
Lymphadenopathy	Arthralgia

Most of these signs and symptoms are due to a bacteraemia and widespread dissemination of *T pallidum*. In our experience, patients do not fit a classical textbook description and therefore a high index of suspicion from the sexual history is required. Table II shows possible differential diagnoses for a secondary syphilitic rash. Any patient who presents with an unexplained rash or genital /oral ulceration should have a sexual history taken to help make an appropriate differential diagnosis. Following secondary syphilis, the infection becomes asymptomatic and enters the **early latent stage**.

Table II Differential Diagnosis for Secondary Syphilis Rash

Scabies	HIV seroconversion
Drug reaction	Psoriasis
Pityriasis rosea	
Pityriasis versicolor	

This stage is still considered to be infectious and is defined as having no physical manifestations of syphilis, positive syphilis serology (positive Immunoglobulin M) and a previous negative syphilis test within the past two years.

Late syphilis is considered to be non-infectious and is divided into four stages: **late latent, gummatous, cardiovascular and neurological**. Further information about each of these is given in Table III.

Table III Stages of Late Syphilis

Late Latent – no signs or symptoms, positive serology and thought to have acquired >2 years ago

Gummatous - Gummas may be multiple or solitary and can affect the skin, mouth, respiratory tract and leg

Cardiovascular

- May present with symptoms from cardiac conduction defect
- Aortic aneurysm – affects proximal ascending aorta
- Aortic regurgitation- usually early diastolic murmur

Neurosyphilis –

- This can also be part of the secondary stage, especially in HIV + patients
- Often asymptomatic
- May present with sudden onset of headache, hemiplegia, aphasia, seizures, cranial nerve palsies, (esp deafness)
- Pupillary abnormalities eg Argyll Robertson pupil (accommodates but doesn't react to light)
- General Paralysis of the Insane
 - Personality change, impaired memory, seizures, tremor, hyperreflexia, extensor plantars
- Tabes Dorsalis
 - "Lightning pains, ataxia, Argyll-Robertson pupils, hyporeflexia, loss of vibration and proprioception/position sense, positive Romberg's sign

Congenital syphilis is divided into early and late. The features of early congenital syphilis (defined as within the first two years of life) normally appear within two to 12 weeks. The signs and symptoms are listed in Table IV.

Late congenital syphilis is diagnosed after two years of age and often there are no signs or symptoms but the diagnosis is made serologically. Table IV lists the signs and symptoms which may be apparent.

The Current Epidemiology of Syphilis in Scotland

In December 2003, Health Protection Scotland (HPS) established National Enhanced Surveillance of Infectious Syphilis Scotland (NESISS).⁴ This collects both laboratory and

Table IV Clinical Features of Early Congenital Syphilis

Failure to thrive	Hepatosplenomegaly
Osteochondritis	Generalised lymphadenopathy
Meningitis	Choroidoretinitis
Nephrotic syndrome	Blood abnormalities e.g. anaemia, thrombocytopenia
Mucosal lesion involving pharynx and nose (snuffles)	Skin lesions: <ul style="list-style-type: none">• Rashes similar to secondary syphilis• Bullous eruptions• Sparse hair

Table V Clinical Features of Late Congenital Syphilis (after the age of 2)

Interstitial keratitis	Paroxysmal Cold Haemoglobinuria
Deafness	Craniofacial malformations e.g. frontal bossing, "saddle nose" deformity
Neurosyphilis	Dental malformations e.g. Hutchinson's incisors
Bilateral painless effusions of knee joints (Clutton's joints)	

clinical information on cases of infectious syphilis (primary, secondary and early latent) and is reported by HPS.⁵ There have been 743 cases reported on NESISS from when it began until December 2006. Six hundred and seventy nine (91%) of these have been in men who have sex with men (MSM), 64 cases in heterosexual men and 35 cases in women.

Of the 217 reported cases in 2006, 183 (84%) were in MSM. The median age of cases was 36 years (range 18 to 72 years).³ Therefore, syphilis unlike many other sexually transmitted infections does not only affect people in the younger age groups. For both the heterosexual and MSM cases, the majority (68%) were presumed to have been acquired through contacts in Scotland. Twenty two per cent of the MSM cases were known to be co-infected with HIV.³

In Scotland, the major burden of infection occurs in the MSM population. Data from specialist gay men's health settings show that patients rarely think that their primary health care provider is aware of their sexuality (Unpublished data, A J Winter). There has been a year-on-year increase in diagnoses in the heterosexual population which could lead to a re-emergence of congenital syphilis.⁵

How Might Syphilis Present in my Practice?

Many practitioners may be seeing patients with syphilis but not recognising the disease. It is important to consider syphilis within a differential diagnosis (see Table II). In our practice we have seen many patients referred in from primary care or hospital practice where the diagnosis has been delayed. These include:

- Genital ulceration thought to be traumatic or herpetic;
- Unexplained skin rashes (thought to be guttate psoriasis, pityriasis);
- Visual loss;
- Hearing loss.

Unlike some other sexual health problems, patients with syphilis can present to a variety of medical and surgical specialties such as:

- Obstetricians (routine antenatal testing);
- Dermatologists;
- Acute medical physicians;
- Neurologists;
- Paediatricians;
- Ear, nose and throat.

The key to recognition is to take a sexual history and a travel history. In cases of suspected congenital syphilis, the mother's sexual and travel history may be relevant.

How Can I Diagnose it?

The diagnosis of syphilis is usually made on a serological blood test as it is not possible to culture the organism. Serological tests for syphilis are divided into non-treponemal (non-specific) tests and treponemal (detect specific treponemal antibody) tests.² (See Table VI).

Table VI Syphilis Serological Tests

Venereal Disease Reference Laboratory	Positive in acute / untreated / resolving infection
Treponema pallidum haemagglutination	Remains positive for life
EIA (IgG/IgM)	Remains positive for life
EIA (IgM)	Remains positive for 1-2 years
InnoLIA Blot	Remains positive for life

Most laboratories use a combined enzyme immunoassay (IgG/IgM) test as the initial "screening" test. If this is positive, further tests are performed in order to confirm the diagnosis. Occasional enzyme linked immunoassay (EIA) positives alone can occur. Here it is important to repeat the tests to look for serological evolution over a month; if no further tests become positive then the reaction is not due to syphilis infection.

Following infection there can be a window period of up to three months before an antibody response is detectable. In suspected early syphilis it is worth asking the laboratory to consider additional tests (such as treponema pallidum (TPPA) and IgM) in case the screening EIA is still negative.

Confirmatory tests include the Venereal Diseases Research Laboratory (VDRL) test and *Treponema pallidum* haemagglutination assay (TPHA). Treponemal specific IgM is detectable for about two years after infection. A specific treponemal blot test (eg InnoLIA) is useful at first diagnosis.

If a suspected chancre is present, fluid from this can be examined for the motile spirochaetes using a technique called dark-ground microscopy (DGM). This technique is only available through your local genitourinary medicine department. In Scotland clinicians now have access to a *T pallidum* polymerase chain reaction test (PCR). This can allow diagnosis of primary syphilis in settings where dark ground microscopy is not possible. Samples in PCR buffer (as for HSV PCR) should be forwarded to the Scottish Bacterial STI Reference Laboratory, Edinburgh.

Lumbar puncture to obtain cerebrospinal fluid (CSF) for serological testing is recommended in certain clinical situations, although guidelines are not that evidence-based. (See Table VII)

Table VII Indications for Lumbar Puncture

Early syphilis (<2 years)	Late syphilis
Neurological symptoms	Neurological symptoms
HIV infection with VDRL>=1:32	HIV infection with VDRL>=1:32
Congenital evaluation	Follow up cannot be assured

Interpreting Syphilis Serology

Syphilis serology is often thought to be difficult to interpret. Some examples are given below. It can be helpful to discuss positive results both with clinical microbiologists and genitourinary medicine specialists. Clinical staging of syphilis can only be done following careful clinical history and examination, not by blood tests alone. Specific treponemal tests generally stay positive for life even after successful treatment. VDRL and IgM resolve after treatment. The VDRL test can be prone to false-positive reactions - these are much less commonly seen now EIA is the routine first screening test. (See Table VIII)

Table VIII Causes for a Biological False Positive VDRL

Acute (<6 months)	Chronic (> 6 months)
Pregnancy	Connective Tissue Disease
Post vaccinations	Autoimmune disorders
Atypical pneumonia	SLE
Malaria	Injecting Drug Use
Bacterial/viral infection	Leprosy
	Older age
	HIV infection

Examples

Case 1

Male patient presents with fever, headache and maculo-papular rash on his chest.

VDRL 1:320

IgM positive

TPPA positive 1:320

EIA IgG/IgM Positive

The above results are consistent with recently acquired syphilis (IgM positive). The clinical picture fits with this.

Diagnosis: Secondary syphilis

Case 2

Female patient presents for antenatal screening. She is originally from Africa. She previously had syphilis and was treated with IM penicillin for 10 days. Her results:

VDRL negative

IgM negative

TPPA positive

EIA IgG/IgM positive

These results are consistent with previously treated syphilis. With treatment, the VDRL should become negative. However the VDRL can also become negative with time. Therefore a treatment history also needs to be taken. If this patient had not had previous treatment, these results would be consistent with untreated latent syphilis.

Case 3

Female caucasian patient attends antenatal clinic for booking bloods. Her results are:

VDRL negative

IgM negative

TPPA negative

EIA IgG/IgM positive

InnoLIA blot indeterminate

This is most likely to be a biological false positive EIA. However, it should be repeated to ensure this is not a case of evolving syphilis before reassuring the patient.

How is it Treated?

Syphilis should ideally be treated with intramuscular injections of long acting penicillin. The dose and duration of treatment depends on the stage of the infection. (See Table IX). Patients should be referred to the genitourinary medicine department for treatment, follow-up and partner notification by the sexual health advisor. For patients with a penicillin allergy, doxycycline can be used but is not as effective. Particular care is needed in treating syphilis.

	HIV negative	HIV positive	HIV untested
Primary/Secondary	Benzathine Penicillin G 2.4MU IM day 1 & 8	Procaine Penicillin 600mg IM for 10 days	Procaine Penicillin 600mg IM for 10 days
Early latent	Benzathine Penicillin G 2.4MU IM day 1 & 8	Procaine Penicillin 600mg IM for 10 days	Procaine Penicillin 600mg IM for 10 days
Late latent	Benzathine Penicillin G 2.4MU IM day 1, 8 and 15	Procaine Penicillin 1.8MU IM and Probenecid 500mg QDS orally for 17 days	Procaine Penicillin 1.8MU IM and Probenecid 500mg QDS orally for 17 days
Neurosyphilis	Procaine Penicillin 1.8MU IM and Probenecid 500mg QDS daily for 17 days (and steroid cover initially)		
Cardiovascular (neurosyphilis excluded)	Procaine Penicillin 1.8MU IM daily for 17 days (and steroid cover initially)		

Partner Notification

Syphilis is sexually transmitted so it is essential that patients are interviewed by a trained sexual health adviser. Partner notification aims to reduce the risk of re-infection to the index case by ensuring assessment and treatment of all current partners. It also allows previous partners to have the opportunity to be tested. In practice, a large proportion of contacts are anonymous and untraceable. In 2006, a total of 840 sexual contacts were reported by the 174 cases who quoted between one and 50 sexual partners during the three months prior to diagnosis. Whilst the majority, (80%) reported fewer than five partners, the percentage of traced contacts decreased from 57% in those reporting fewer than five partners to 20% when five or more partners were reported.³

Follow Up

Following completion of treatment, all patients should have regular serological follow-up as per national guidelines to ensure that treatment has been successful and there has been no relapse or re-infection.⁶ Follow-up for HIV negative patients can usually be discontinued after one year.

Relapse/Re-infection

In a number of cases the VDRL titre fails to fall by more than four-fold or rises again following a fall. It is currently not possible to distinguish between relapse or re-infection other than by a careful and sensitive clinical history. Re-treatment is recommended in this situation.

HIV Patients

All patients diagnosed with syphilis should have HIV testing after appropriate pre-test discussion. Patients who are co-infected are at risk of faster disease progression and there is still some debate as to whether all HIV patients with early syphilis should be offered a lumbar puncture to exclude neurosyphilis.⁷ In known HIV positive patients, national guidelines recommend that syphilis serology is checked at three monthly intervals in outbreak situations.⁷ Often syphilis will present atypically in immunocompromised patients. Following treatment of syphilis, all HIV positive patients should have life-long serological follow-up.

Syphilis in Pregnancy

All pregnant women should be screened for syphilis at the initial antenatal visit.⁶ In pregnant women with untreated early syphilis, 70-100% of infants will be infected, with stillbirths in up to one third of cases.⁶ Infection of the foetus seldom occurs before the 18th week but may occur as early as the ninth week.⁸ Other complications which may arise are premature delivery, perinatal death and congenital syphilis. These are more likely to occur in the early stages of syphilis. It is still possible for the foetus to be infected despite treatment. Women who have had documented treatment for syphilis in the past do not need re-treatment during current or subsequent pregnancies if there is no clinical evidence of syphilis and the VDRL titre is negative or serofast in low titre compared to previous results.⁶ However it is important that re-infection is excluded by checking the partner, and babies should be followed-up by a paediatrician to exclude congenital syphilis as per national guidelines.⁶

What Should Be Done if a Patient Receives a Positive Syphilis Result?

Any positive syphilis results should ideally be discussed with a genitourinary medicine physician to decide on the stage of infection and further management. A positive syphilis serology should be repeated to ensure the result is accurate and belongs to that patient. Patients also need to be referred for sexual health screening to exclude concomitant infections and see a sexual health advisor for partner notification.

Table X Syphilis Serology Through the Various Stages

Test	Primary	Secondary	Early latent	Late latent
EIA	+/-	++	++	++
IgM	+	++	+/-	-
VDRL	+/-	+++	+	+
TPPA	+/-	+++	+++	+++

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