

UK national guidelines on the management of syphilis 2015

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Abstract

These guidelines are an update for 2015 of the 2008 UK guidelines for the management of syphilis. The writing group have piloted the new BASHH guideline methodology, notably using the GRADE system for assessing evidence and making recommendations. We have made significant changes to the recommendations for screening infants born to mothers with positive syphilis serology and to facilitate accurate and timely communication between the teams caring for mother and baby we have developed a birth plan. Procaine penicillin is now an alternative, not preferred treatment, for all stages of syphilis except neurosyphilis, but the length of treatment for this is shortened. Other changes are summarised at the start of the guideline.

Keywords

Syphilis, diagnosis, treatment

Date received: 5 November 2015; revised: 1st December 2015; accepted: 2 December 2015

New in the 2015 guidelines

Important changes

- Procaine penicillin is now an alternative treatment where benzathine penicillin is suitable. This is due to the pain associated with treatment courses requiring multiple injections and inconvenience and cost for patients and staff.
- Resistance to macrolide antibiotics limits their utility; they are to be used only when there are no suitable alternatives and with assured follow-up.
- In asymptomatic disease there is no need for full routine examination or chest X-ray (CXR).
- Amended recommendation to period of sexual abstinence following treatment of early infectious syphilis.
- The duration for the recommended treatment of neurosyphilis is changed to 14 days, consistent with expert opinion and other guidelines.
- Amended minimal follow-up recommendations.
- Some neonates will not need serology following delivery.

- Inclusion of a syphilis birth plan.
- Clear graded recommendations at the end of each section, using the GRADE system.

Objectives

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications

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NICE has accredited the process used by BASHH to produce its European guideline for the management of syphilis. Accreditation is valid for 5 years from 2011.
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that can arise in people either presenting with signs and symptoms of an STI or undergoing investigation for possible infection.

Specifically, this guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of syphilis, covering the management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (although there is a section referring to the management of congenital syphilis [CS] in children) presenting to health-care professionals, working in departments offering level 3 care in STI management within the United Kingdom.¹ However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

The recommendation of this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

Search strategy

The previous UK and USA guidelines for the management of syphilis were reviewed.^{2,3}

Literature reviews included searching Medline for the years 2007 to 2014 and the Cochrane library using the keywords 'syphilis' and 'syphilis and HIV' plus additional MeSH headings 'neurosyphilis', 'cardiovascular syphilis', 'latent syphilis' and 'syphilis and treatment'. A search on Embase from 2007–2014 was also conducted. Only English language papers were used.

Methods

The guidelines writing group piloted an updated version of the BASHH Framework for Guideline Development. The previous version last published in 2010 is available at: <http://www.bashh.org/documents/2926> (last accessed 19 January 2013). Following piloting of this updated framework, incorporating feedback from this and another group of guideline authors, the updated framework will be published. The major change is the adoption of the GRADE system for assessing evidence (<http://www.gradeworkinggroup.org/index.htm>) [last accessed 19 January 2014].

Equality impact assessment

This was completed using the NICE tool for this accessed at: <http://www.nice.org.uk/media/4DC/76/>

Item62_NEquIATTopicSelectionSMTAppB221107.pdf and is an appendix to this document.

Stakeholder involvement, piloting and feedback

The document was reviewed by the Clinical Effectiveness Group of BASHH, and their comments incorporated. The draft guideline was placed on the BASHH website and any comments received after two months were reviewed by the authors and acted on appropriately. The document was also piloted by target users and the public panel of BASHH, and their feedback considered by the authors.

Aetiology, transmission and epidemiology

- Syphilis is caused by infection with the spirochete bacterium *Treponema pallidum* subspecies *pallidum*.⁴
- It is transmitted by direct contact with an infectious lesion or by vertical transmission (trans-placental passage) during pregnancy.⁵ Approximately one-third of sexual contacts of infectious syphilis will develop the disease (transmission rates of 10–60% are cited).^{6,7}
- Site of bacterial entry is typically genital in heterosexual patients, but 32–36% of transmissions among men who have sex with men (MSM) may be at extra-genital (anal, rectal, oral) sites through oral-anal or genital-anal contact.⁸ In one study, oral sex accounted for 13.7% of syphilis transmissions, particularly in MSM.⁹ Injecting drug use (sharing needles) and blood transfusion (rare as routine screening is performed in the UK and treponemal survival beyond 24–48 h at 4°C is unlikely) are also potential routes of transmission.^{10,11}
- *T. pallidum* readily crosses the placenta and vertical transmission can occur at any stage of pregnancy. The risk of transmission varies with syphilis stage and is greatest in early disease.^{12,13} Accordingly, transmission was associated with rapid plasma reagin (RPR) titres ≥ 8 (RR 18.1, $p < 0.001$) in one cohort study.¹⁴
- Syphilis predominates among white MSM aged 25–34, many of whom (40%) are HIV-1 co-infected. In 2014, there were 4317 cases of infectious syphilis, of which 3477 cases were in MSM. Compared with 2013, this represents a 46% rise among MSM and a 33% rise overall.¹⁵ There were 263 cases in women in 2014. Rates of CS are correspondingly low (0.0025/1000 live births in 2011) and predominantly among chaotic and socio-economically deprived women presenting to antenatal services in the third trimester.^{15,16}

Classification and clinical features

- Syphilis is a multi-stage, multi-system disease, which is broadly defined as congenital or acquired.

Acquired (adult) disease

Early disease

- Following contact, *T. pallidum* invade through the mucosal surface or abraded skin and divide at the point of entry to produce the chancre of primary disease. This incubation period is typically 21 days (range 9–90), but is dependent on infectious dose – larger doses resulting in ulcers more quickly.^{7,17} Primary syphilis is characterised by a single papule and moderate regional lymphadenopathy. The papule subsequently ulcerates to produce a chancre, which is classically anogenital (penile, labial, cervical or peri-anal), single, painless and indurated with a clean base discharging clear serum but not pus. However, chancres may also be multiple, painful, purulent, destructive, extra-genital (most frequently oral) and may cause the syphilitic balanitis of Follmann.^{18,19} When present at extra-genital sites and painless, they may pass unnoticed. In the context of HIV-1 co-infection, they may be multiple, deeper and persist into the secondary stage of disease.²⁰ Early after infection, the bacteria disseminate widely via blood and lymphatics. They are subject to local immune clearance and ulcers resolve over 3–8 weeks.
- Untreated, 25% of patients will develop signs of secondary syphilis approximately 4–10 weeks after the appearance of the initial chancre.^{21,22} Secondary syphilis is multi-system and typically occurs three months after infection.⁵ It often presents with a widespread mucocutaneous rash and generalised lymphadenopathy. The rash may be maculo-papular (50–70%), papular (12%) or macular (10%) and it may, but does not usually, itch.^{21,23,24} It can affect the palms and soles (11–70%) and hair follicles, resulting in alopecia. Two more important mucocutaneous signs are mucous patches (buccal, lingual and genital) and highly infectious condylomata lata affecting warm, moist areas (mostly the perineum and anus).^{8,23} HIV-1 infection does not appear to impact on the mucocutaneous manifestations of secondary syphilis.²⁵ Secondary syphilis may result in hepatitis; glomerulonephritis (mediated by antibody-treponeme complex deposition) and splenomegaly.^{26–28} A small proportion of patients (1–2%) will develop neurological complications during secondary syphilis.²¹ These are typically acute meningitis

(headache, neck stiffness, photophobia, nausea) and cranial nerve palsies including eighth nerve palsy with resultant hearing loss and possible tinnitus.²⁹ Eye involvement may result in uveitis (most commonly posterior), optic neuropathy, interstitial keratitis and retinal involvement.³⁰

Latent disease

- Secondary syphilis will resolve spontaneously in 3–12 weeks and the disease enters an asymptomatic latent stage.²¹ This is defined as early within two years, and late thereafter (ending with the development of tertiary disease). The distinction between early and late latent disease is somewhat arbitrary, but important as approximately 25% of patients will develop a recurrence of secondary disease during the early latent stage.²²

Late (tertiary) disease

- Late disease occurs in approximately one-third of untreated patients around 20–40 years after initial infection. It is divided into gummatous disease (15% of patients); cardiovascular (10%) and late neurological complications (7%).²² The clinical manifestations of late syphilis are highly variable and are rarely seen due to the use of treponemocidal antibiotics for other indications. The clinical features of symptomatic late syphilis are summarised in Table 1.

Gummatous disease

- In the Oslo study, 15% of patients developed gummatous disease.²² These granulomatous lesions with central necrosis can occur within two years of latency, but are typically seen after an average 15 years.⁵ They can occur anywhere, but most often affect skin and bones. They rapidly resolve on administration of therapy.

Cardiovascular disease

- Cardiovascular syphilis typically occurs 15–30 years after infection. It only becomes symptomatic or complicated in 10% of patients.²² The ascending aorta is the predominant site of damage resulting in dilatations and aortic valve regurgitation. Rarely, the coronary ostia may become involved and saccular aneurysms may develop.³¹

Table 1. Clinical features of symptomatic late syphilis.

	Timing after infection	Signs and symptoms
Neurosyphilis		
Asymptomatic	Early/late	Abnormal CSF with no signs/symptoms; this is of uncertain significance given that CSF abnormalities have been found in up to 30% of primary and secondary syphilis yet this does not become clinically significant in the majority of patients.
Meningovascular	2–7 years	Focal arteritis inducing infarction/meningeal inflammation; signs dependent on site of vascular insult. Occasional prodrome; headache, emotional lability, insomnia.
Parenchymous		
• General paresis	10–20 years	Cortical neuronal loss; gradual decline in memory and cognitive functions, emotional lability, personality change, psychosis and dementia. Seizures and hemiparesis are late complications.
• Tabes dorsalis	15–25 years	Inflammation of spinal dorsal column/nerve roots; lightning pains, areflexia, paraesthesia, sensory ataxia, Charcot's joints, mal perforans, optic atrophy, pupillary changes (e.g. Argyll Robertson pupil).
Cardiovascular	10–30 years	Aortitis (usually ascending aorta); asymptomatic, substernal pain, aortic regurgitation, heart failure, coronary ostial stenosis, angina, aneurysm.
Gummatous	1–46 years (average 15)	Inflammatory granulomatous destructive lesions; can occur in any organ but most commonly affect bone and skin.

CSF: cerebrospinal fluid.

Neurological disease

Meningovascular syphilis

- Typically, 5–10 years after infection (may be earlier). Not typically considered to be tertiary disease
- Infectious arteritis which may result in ischaemic stroke (middle cerebral artery territory most commonly affected)
- Prodrome may occur in the weeks/months prior to stroke including headache, emotional lability and insomnia

General paresis

- Progressive dementing illness 10–25 years after infection secondary to cortical neuronal loss
- Initial forgetfulness and personality change which develop into severe dementia. Seizures and hemiparesis may occur (late)

Tabes dorsalis

- 15–25 years after infection (longest of neurological complications)
- Characterised by sensory ataxia and lightning pains

- Pupillary abnormalities common (Argyll-Robertson)
- Dorsal column loss (absent reflexes, joint position and vibration sense)

Congenital syphilis

- CS is divided into early (diagnosed in the first two years of life) and late (presenting after two years). The presence of signs at the time of delivery is dependent on the duration of maternal infection and the timing of treatment. Around two-thirds of infants with CS will be asymptomatic at birth but most will develop signs by five weeks.^{32,33}

Early CS (within two years)

- Common manifestations (40–60% will have one) include: rash, haemorrhagic rhinitis (bloody snuffles), generalised lymphadenopathy, hepatosplenomegaly and skeletal abnormalities³³
- Other signs include: condylomata lata, vesiculobullous lesions, osteochondritis, periostitis, pseudoparalysis, mucous patches, perioral fissures, non-immune hydrops, glomerulonephritis, neurological or ocular involvement, haemolysis and thrombocytopenia

Late congenital syphilis

- Signs develop as a result of chronic and persistent inflammation resembling gummatous disease in adults. Stigmata of congenital infection includes: interstitial keratitis; Clutton's joints; Hutchinson's incisors; mulberry molars (maldevelopment of cusps of first molars); high palatal arch; rhagades (peri-oral fissures); sensorineural deafness; frontal bossing; short maxilla; protuberance of mandible; saddle nose deformity; sterno-clavicular thickening; paroxysmal cold haemoglobinuria; neurological involvement (intellectual disability, cranial nerve palsies).^{33,34}

Clinical diagnosis

History

- A full and accurate history is important to identify potential complications of symptomatic infection (both early and late) and to distinguish between late latent, previously treated and non-venereal *T. pallidum* infection (yaws, pinta, bejel), which may have identical serological results
- Full sexual history:
 - For primary syphilis – to include all sexual partners in the last three months
 - Early secondary and early latent syphilis – all partners in the last two years
 - For late syphilis – according to history and previous treponemal serology, lifetime partners and possibly children
- Directly question for symptoms of syphilis
- Fully explore previous syphilis diagnoses:
 - Year and place of diagnosis
 - Treatment received (drug, route, duration)
 - Serological results (contact treating centre if necessary/possible)
- Previous syphilis testing (with consideration of the screening tests used at the time):
 - Antenatal screening
 - Blood donation
 - Sexual health screening
- Potential for previous infection with non-venereal *T. pallidum* infection:
 - Childhood skin infections (yaws)
 - Previously resident in an endemic area/country
- Full obstetric history (where appropriate):
 - Adverse pregnancy outcomes (which may be due to syphilis)
 - Identify live births and children who may have late congenital disease

Examination

- Early disease (primary or secondary) to include the following, when indicated:
 - Genital examination
 - Skin examination including eyes, mouth, scalp, palms and soles
 - Neurological examination if neurological symptoms elicited
- Symptomatic late disease (including suspected late congenital disease); clinical examination should be undertaken as indicated, with attention to:
 - Skin
 - Musculoskeletal system (congenital)
 - Cardiovascular system (for signs of aortic regurgitation)
 - Nervous system (general paresis: dysarthria, hypotonia, intention tremor, and reflex abnormalities; Tabes dorsalis: pupil abnormalities, impaired reflexes, impaired vibration and joint position sense, sensory ataxia and optic atrophy)

Laboratory diagnosis

Demonstration of *T. pallidum* from lesions or infected lymph nodes

- Dark ground microscopy:³⁵
 - Should be performed by experienced observers
 - Is less reliable in examining rectal and non-penile genital lesions and not suitable for examining oral lesions due to the presence of commensal treponemes
- Polymerase chain reaction (PCR):^{36–38}
 - Can be used on oral or other lesions where commensal treponemes may also be present
 - Available at reference laboratories
 - In certain circumstances, PCR may be helpful in diagnosis by demonstrating *T. pallidum* in tissue samples, vitreous fluid and cerebrospinal fluid (CSF)^{39–42}

Recommendations

- Where appropriate expertise and equipment are available, perform dark ground microscopy on possible chancres: 2A.
- *T. pallidum* testing by PCR is appropriate on lesions where the organism may be expected to be located: 1A.

Serological test for syphilis

- Treponemal antibody tests cannot differentiate syphilis (caused by infection with *T. pallidum* subspecies *pallidum*) from the endemic treponematoses, yaws (caused by infection with *T. pallidum* subspecies *per-tenuis*), bejel (or endemic syphilis, caused by infection with *T. pallidum* subspecies *endemicum*) and pinta (caused by infection with *T. pallidum* subspecies *car-ateum*). Positive treponemal serology in patients from a country with endemic treponemal infection should therefore be investigated and treated for syphilis as a precautionary measure, unless they have been adequately treated for syphilis previously.⁴³
- Treponemal antibody tests can be classified into:
 - Non-specific (cardiolipin, lipoidal, reagin or non-treponemal) tests: Venereal Diseases Research Laboratory (VDRL) carbon antigen test/RPR test.
 - Specific (treponemal) tests: treponemal enzyme immunoassay (EIA) or treponemal chemiluminescent assay (CLIA); *Treponema pallidum* haem-agglutination assay (TPHA); *Treponema pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorption test (FTA-abs), *Treponema pallidum* immunoblot. Most of these tests are now based on recombinant treponemal antigens and detect treponemal IgG and IgM antibody.
 - *T. pallidum*-specific IgM antibody tests: anti-treponemal IgM EIA and immunoblot.

Primary screening tests

- Treponemal EIA/CLIA (preferably a test that detects both IgG and IgM) or TPPA, which is preferred to TPHA.
- Request an anti-treponemal IgM test if primary syphilis is suspected. The clinical utility of the IgM test is limited by its suboptimal sensitivity and it should not be used to stage disease or decide the duration of treatment required.⁴³
- Rapid treponemal tests might be useful in some out-reach settings, provided positive results are confirmed by laboratory tests.⁴³

Confirmatory tests

- Positive screening tests should be confirmed with a different treponemal test.
- An IgG immunoblot is recommended as a supplementary confirmatory test when the standard confirmatory test does not confirm the positive screening test result. The FTA-abs is not

recommended as a standard confirmatory test, although it may have a role in specialist laboratories.

- A second specimen should always be tested to confirm positive results, and on the day that treatment is commenced so the peak RPR/VDRL is documented.

Tests for assessing serological activity of syphilis

- A quantitative RPR/VDRL should be performed when treponemal tests indicate syphilis as this helps stage the infection and indicates the need for treatment in some cases, for example, where the patient has been previously treated and may have been re-infected.⁴³
- An initial RPR/VDRL titre of >16 usually indicates active disease and the need for treatment, although serology must be interpreted in the light of the treatment history and clinical findings.⁴⁴
- A RPR/VDRL titre of 16 or less does not exclude active infection, particularly in a patient with clinical signs suggestive of syphilis or where adequate treatment of syphilis is not documented.
- A negative anti-treponemal IgM test does not exclude active infection, particularly in late disease.

Tests for monitoring the effect of treatment

- A quantitative RPR/VDRL test is recommended for monitoring the serological response to treatment and should be performed on a specimen taken on the day that treatment is started as this provides an accurate baseline for monitoring response to treatment.

Repeat screening is recommended

- Six and 12 weeks after a single 'high risk' exposure (unprotected oral, anal or vaginal intercourse with homosexual man, multiple partners, anonymous sex in saunas and other venues, commercial sex worker or sex partner linked with a country where the prevalence of syphilis is known to be high).
- In individuals at ongoing risk due to frequent 'high risk' exposures as defined above, screening as part of routine sexual health check-ups for all STIs including HIV and others is recommended, usually every three months and informed by sexual history.
- Two weeks after presentation in those with dark field or PCR negative ulcerative lesions that could be due to syphilis.

False-negative syphilis serology

- Treponemal screening tests are negative before a chancre develops and may be for up to two weeks afterwards.
- A false-negative RPR/VDRL test may occur in secondary or early latent syphilis due to the prozone phenomenon when testing undiluted serum, in such cases negative tests on undiluted sera should be repeated on diluted sera.⁴⁵ This may be more likely to occur in HIV-infected individuals.⁴⁶
- The RPR/VDRL and IgM may be negative in late syphilis.⁴²

False-positive syphilis serology

- Occasional false-positive results may occur with any of the serological tests for syphilis.
- In general, false-positive reactivity is more likely in autoimmune disease, older age and injecting drug use.
- In the absence of symptoms of syphilis, a history of syphilis or a concomitant positive anti-treponemal IgM; transient or persistent reactivity in a single treponemal antigen test should be considered to be a false-positive result.

Recommendations

- An EIA/CLIA, preferably detecting both IgM and IgG IS the screening test of choice: 1B.
- Positive screening tests should be confirmed with a different treponemal test (not the FTA-abs) and a second specimen for confirmatory testing obtained: 1B.
- A quantitative RPR or VDRL should be performed when screening tests are positive: 1A.
- Repeat negative serological tests for syphilis (STS):
 - At six and 12 weeks after an isolated episode which is high risk for exposure to syphilis,
 - At two weeks after possible chancres that are dark-ground and/or PCR negative are observed: 1B.

Evaluation of neurological, cardiovascular or ophthalmic involvement

- CXR in late latent syphilis is not recommended as a routine investigation.⁴⁷ Patients with syphilis who have symptoms or signs of cardiovascular involvement should have a full cardiovascular assessment.
- Patients should have a thorough neurological examination if they have symptoms suggestive of neurological involvement.⁴⁸

- Computed tomography (CT) or magnetic resonance imaging (MRI) imaging of the brain should be considered if symptoms or signs are present, with one of these being performed and reviewed prior to lumbar puncture.
- Routine CSF examination of patients with latent syphilis is not recommended.^{49,50}
- Serum RPR/VDRL titre may offer some guidance as to whether or not a lumbar puncture should be undertaken. In a retrospective study of patients with latent syphilis, a negative VDRL in the peripheral blood was found to have 100% sensitivity in excluding CSF abnormalities compatible with the diagnosis of neurosyphilis,⁵¹ whereas a serum RPR of $\geq 1:32$ has been demonstrated to predict CSF abnormalities compatible with neurosyphilis.⁵²
- Indications for CSF examination in late syphilis infection include: where there is clinical suspicion of neurosyphilis or treatment failure.

Interpretation of CSF serology

- CSF serology should be interpreted in conjunction with the clinical presentation of the patient. The tests we have are better at excluding neurosyphilis than helping to diagnose it. However, no CSF test result can definitively exclude a diagnosis of neurosyphilis.⁵³ Definitive diagnosis of neurosyphilis is histological, usually an impossibility in practice. CSF tests can only support clinical diagnosis.
- In order for these tests to be interpreted accurately, it is vital that the CSF is not macroscopically contaminated with blood.⁵⁴ Positive syphilis tests on CSF should be interpreted in conjunction with biochemical examination of the CSF as well as clinical signs and symptoms.
- The majority of individuals who have symptomatic neurosyphilis have a raised white cell count (>5 cells/mm) in the CSF, though in cases of parenchymous neurosyphilis this may not be the case.⁴³
- The overall sensitivity of the CSF VDRL/RPR is affected by the stage of syphilis. The RPR is less sensitive than the VDRL, with a range of 10% for asymptomatic cases to 90% for symptomatic cases.⁵⁵
- In the CSF, the RPR is less sensitive than the VDRL. Both tests are relatively insensitive in CSF so false-negatives are common.⁵⁶
- A negative treponemal test on CSF makes a diagnosis of neurosyphilis unlikely but does not exclude the diagnosis.⁵³ A positive test is highly sensitive for neurosyphilis but lacks specificity because reactivity may be caused by transudation of immunoglobulins from the serum into the CSF⁵⁷ or by leakage

Table 2. The CSF criteria supporting a diagnosis of neurosyphilis (58, 136).

CSF parameters	In HIV-negative individuals	In HIV-positive individuals
WBC	>5 μ L	>20 μ L OR 6–20 μ L (on ART/plasma HIV VL undetectable, or blood CD4 < 200)
Protein	>0.45 g/l	>0.45 g/l
RPR/VDRL	+	+
TPPA	>1:320	>1:320

ART: antiretroviral therapy; TPPA: *Treponema pallidum* particle agglutination assay; VDRL: Venereal Diseases Research Laboratory; RPR: rapid plasma reagin; CSF: cerebrospinal fluid.

through a damaged blood–brain barrier resulting from conditions other than syphilis.

- The suboptimal sensitivity and specificity of *T. pallidum* PCR on CSF means that it is currently considered unhelpful in this circumstance.⁴³
- In HIV-positive patients who are not co-infected with syphilis, CSF WBC >5 is associated with: CD4 <200 or HIV viral load (VL) >40 or not taking antiretroviral therapy (ART). Thus, a CSF pleocytosis in patients on ART, or with plasma HIV VL <40 or peripheral blood CD4 >200 are more likely to be due to neurosyphilis rather than HIV infection.⁵⁸
- The CSF criteria supporting a diagnosis of neurosyphilis are summarised in Table 2.

Diagnosis of cardiovascular syphilis

- This diagnosis is made by the presence of the typical clinical features of cardiovascular syphilis (see Table 1) combined with positive syphilis serology. Patients with suspected cardiovascular syphilis need assessment by a cardiologist.

Diagnosis of gummata

- Diagnosis of syphilitic gummata is usually made on clinical grounds; typical nodules/plaques or destructive lesions in individuals with positive syphilis serology. Histological examination of a lesion may suggest this diagnosis and *T. pallidum* may be identified within the nodules by PCR.

Recommendation

- Those with possible gummatous, neurological or cardiovascular symptoms or signs require

examination and further evaluation by appropriate specialists: 1C.

Diagnosis of CS

- Direct demonstration of *T. pallidum* by dark ground microscopy and/or PCR of exudates from suspicious lesions, or body fluids, e.g. nasal discharge.⁵⁹
- Serological tests should be performed on infant's blood not cord blood, and if the infant's serum is positive on screening, perform treponemal IgM EIA, quantitative RPR/VDRL and quantitative TPPA tests on the infant and mother in parallel. Serological tests detecting IgG may be positive due to passive transfer of maternal antibodies whether or not the infant is infected.
- The following, if confirmed on testing a second specimen from the infant, indicate a diagnosis of congenital infection
 - A positive IgM EIA test,^{59,60}
 - A positive RPR/VDRL test on CSF,
 - A four-fold or greater difference of RPR/VDRL titre or TPPA titre above that of the mother,
 - A four-fold or greater increase in RPR/VDRL or TPPA titre within three months of birth,
 - In a child more than 18 months age, positive treponemal tests.
- Further investigations may be required:
 - Blood: full blood count, liver function, electrolytes,
 - CSF: cells, protein, serological tests,
 - X-rays of long bones,
 - Ophthalmic assessment as indicated.

Recommendation

- Infants with possible signs of CS require appropriate evaluation and testing in conjunction with maternal STS and treatment history: 1A.

Diagnosis in HIV-positive individuals

- Both treponemal and non-treponemal serologic tests behave in the same manner as in HIV-negative individuals. Unusual serologic responses, such as false-negative and delayed seroreactivity have been observed in HIV-infected individuals.^{61–63}
- Patients with neurological signs and symptoms (including ophthalmic involvement) should be

investigated for neurosyphilis with CSF examination. Pleocytosis and raised protein levels are commonly seen in HIV-positive patients even without syphilis neurological involvement.

- Patients with advanced HIV infection/immunosuppression (CD4 count <350 cells/cmm) and higher serum RPR/VDRL titre ($\geq 1:32$) are more likely to have clinical and CSF abnormalities consistent with neurosyphilis.^{52,64,65}

Management: General considerations

- All patients should be offered screening for other STIs including HIV.
- Patients should be given a detailed explanation of syphilis, including the long-term implications for the health of themselves and their partners/families. This should be reinforced by giving them access to clear and accurate written information.
- There is very little evidence to inform advice about the time sexual abstinence is recommended following treatment, however, patients should be advised to refrain from sexual contact of any kind until the lesions of early syphilis (if they were present) are fully healed and until two weeks following treatment completion.
- A treponemicidal level of antimicrobial should be achieved in serum, and in the case of neurosyphilis, in the CSF. A penicillin level of >0.018 mg/l is considered treponemicidal,⁶⁶ but a higher concentration might be preferable for more rapid elimination of treponemes. The maximal elimination effect is attained at a level of 0.36 mg/l.⁶⁷
- Duration of treponemicidal levels of antimicrobial should be at least seven days to cover a number of division times (30–33 h) of treponemes in early syphilis with a subtreponemicidal interval of not more than 24–30 h.⁶⁶
- Longer duration of treatment is given in late syphilis on the basis of more slowly dividing treponemes in late syphilis. Treponemes may persist despite apparently successful treatment indicating that some treponemes may be 'resting' or dividing very slowly.^{68–73}
- Clinical data are lacking on the optimal dose and duration of treatment and the long-term efficacy of antimicrobials other than penicillin. The recommendations are based mainly on laboratory considerations, biological plausibility, expert opinion, case studies and clinical experience.
- Parenteral rather than oral treatment has been the treatment of choice because therapy is supervised and bioavailability is guaranteed.
- Non-penicillin antibiotics that have been evaluated include doxycycline, erythromycin and azithromycin. Erythromycin is least effective and does not penetrate the CSF or placental barrier well.^{74,75} Doxycycline has superseded the older tetracyclines; although 100 mg once or twice daily for 14 days is effective⁷⁶ failure of once daily doxycycline has been reported.⁷⁷ Two studies of a single dose of 2 g of azithromycin have shown efficacy in early syphilis equivalent to that of benzathine penicillin.^{78,79} However, there are concerns regarding azithromycin treatment failure which appears to be linked to intrinsic macrolide resistance in some strains of *T. pallidum*.^{80–83} Consequently, macrolide therapies should be used only as a last resort and when close follow-up can be ensured.
- In small studies, a number of ceftriaxone regimens have been shown to be effective^{84–91}
- The host immune response is important as 60% of untreated individuals go through life without developing late complications.²²
- Although both benzathine penicillin G and standard regimens of procaine penicillin G do not achieve treponemicidal levels in CSF^{92–97} and CSF involvement is common in early syphilis, CSF abnormalities are uncommon after recommended treatment of early syphilis. The prevalence of late syphilis including neurosyphilis remains low indicating that treatment is effective and suggests that host immune responses in early syphilis play an essential part. A single dose of 2.4 MU benzathine penicillin G in asymptomatic neurosyphilis showed a 21% CSF relapse rate which was twice that of other penicillin preparations⁹⁸.
- Cardiovascular and neurological lesions may progress despite adequate treatment for syphilis. Steroids should be given with all anti-treponemal antibiotics for neurological and cardiovascular syphilis.
- For neurosyphilis 2.4 g (2.4 MU) IM OD for 10–14 days of procaine penicillin (plus probenecid 500 mg PO QDS for the same duration) is the favoured outpatient regime dose in the CDC 2010 guidelines³ as it has been shown to produce treponemicidal levels in the CSF,⁹⁹ although this may be an inconsistent finding.¹⁰⁰ It is likely that lower doses of procaine penicillin are as efficacious.¹⁰¹ No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients (although some treatment failures have been¹⁰²).
- Both benzathine and procaine penicillins and probenecid are unlicensed in the UK. Practically, this means that:

- The prescriber should be aware that the product is unlicensed and ensure that they are aware of the uses and actions of the product and is assured of its quality and source.
- The use of the unlicensed medicine is justified by the clinical condition of the patient.
- Legal responsibility for prescribing falls to the doctor who signs the prescription.
- The unlicensed status of the medicine should be explained to the patient and the service's policy relating to informed patient consent is complied with.
- Records are made in the patient's medical notes of the unlicensed medicine and the indication for use.
- Incidents of unexpected adverse patient reactions are recorded and reported to the CSM via the yellow card scheme and to the Trust's critical incident report scheme.
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- Incidents of unexpected adverse patient reactions are recorded and reported to the CSM via the yellow card scheme and to the Trust's critical incident report scheme.
- pericardial effusion and skin oedema). It may also be associated with placental oedema.
- Significance of positive maternal treponemal serology:
 - In 2011 in the UK, approximately one woman in 650 (0.15%) had positive antenatal screening tests. Of these:
 - 46% had been treated adequately for syphilis before conception.
 - 23% had false-positive tests.
 - 21% were diagnosed and treated for syphilis for the first time during the current pregnancy.¹⁰⁴
- Management of positive maternal treponemal serology.
 - It is essential that women with positive screening tests are referred as quickly as possible to a genitourinary (GU) physician. This requires clear and timely communication between the screening laboratory, midwifery and obstetric services, GU medicine and paediatrics. Many hospitals will have a multi-disciplinary team (MDT) to manage pregnancies complicated by HIV infection, and it may be most appropriate that due to established working relationships, the HIV MDT manages cases of syphilis in pregnancy. GU physicians who have little experience of managing syphilis in pregnancy should seek advice from more experienced colleagues or from clinical networks.
 - Management where syphilis was cured prior to current pregnancy.
 - RPR/VDRL titres should be checked at first antenatal booking appointment, and if there is risk of re-infection repeated later in pregnancy. If the RPR/VDRL excludes re-infection, the woman requires no further treatment and there is no need for the neonate to undergo tests for syphilis.

Recommendations

- All patients with syphilis should have screening for other STIs including HIV: 1A.
- Patients should be given a clear explanation of their diagnosis of syphilis and its implications, reinforced with written information: 1D.
- Patients with early, infectious syphilis should be advised to abstain from sex until any lesions (if any) have resolved or until two weeks after treatment completion: 1C.
- Parenteral treatment with the appropriate penicillin preparation is the treatment of choice: 1B.
- Macrolide antibiotics are to be used if only available option and when follow-up can be assured: 1B.

Management in pregnancy: General considerations

- All pregnant women should have serological screening for syphilis at their first antenatal assessment. Tests should be repeated later in pregnancy if a woman has been at risk of infection after a negative initial screen. Such cases should be discussed with a local GU medicine physician.
- Adverse pregnancy outcomes in syphilis:
 - Although fetal infection usually occurs late in pregnancy, it has been demonstrated as early as 8–9 weeks of gestation.¹⁰³ This may result in polyhydramnios, miscarriage, pre-term labour, still-birth and hydrops (oedema in two or more fetal compartments, e.g. ascites, pleural effusion,
- Referral to fetal medicine:
 - Where syphilis is treated in this pregnancy, particularly when this is early infection, maternal referral to fetal medicine is recommended when 26 weeks' gestation has been reached prior to treatment. Fetal syphilis infection may be suggested by ultrasound scan detection of non-immune hydrops or hepatosplenomegaly. Fetal assessment will help planning of antepartum care as well as neonatal treatment.
- Re-treatment of women with a history of syphilis treated before conception. This should be considered when:
 - There is uncertainty about the adequacy of treatment on history,
 - Serological cure (a four-fold drop in RPR/VDRL titre, e.g. from 16 to 4) did not occur. Where low level RPR/VDRL titres are present at baseline,

this drop may not occur and the titres may remain serofast.

- Maternal diagnosis
 - It is vital that GU physicians make a clear maternal diagnosis and communicate this to the multi-disciplinary team. A template syphilis birth plan is attached as an appendix. The outcome could be:
 - *Maternal treatment not indicated*
 - Biological false-positive test,
 - Syphilis adequately treated before this pregnancy.
 - *Maternal treatment indicated*
 - Active syphilis of any stage,
 - Unclear history of syphilis treated prior to this pregnancy.
 - Maternal treatment
 - A single dose of benzathine penicillin G 2.4 MU is effective in most cases.^{14,105,106} Although treatment failures have been described in case reports and small series, these are mainly in those at increased risk of transmission (higher RPR/VDRL titre, maternal primary and secondary syphilis and when treatment was commenced in the third trimester).^{13,107}
- Physiological changes in pregnancy alter drug pharmacokinetics and may cause reduced plasma penicillin concentrations.¹⁰⁸ For this reason, when treatment is initiated in the third trimester, a second dose of benzathine penicillin is recommended one week after the first, with careful assessment of the neonate at birth.
- Non-penicillin alternatives include ceftriaxone, for which there are limited data¹⁰⁹ and erythromycin or azithromycin. There are no studies evaluating azithromycin in pregnancy, and treatment failure has been reported with erythromycin^{110,111} and azithromycin,¹¹² with uncertain placental penetration of these antibiotics.^{74,75} For these reasons, treatment of the baby at birth with penicillin is recommended following maternal treatment with macrolides.
- De-sensitisation to penicillin with immediate subsequent penicillin treatment in those reporting allergy should be considered.¹¹³
- Management should be in close liaison with obstetric, midwifery and paediatric colleagues.
- In pregnancy, the rate of the Jarisch-Herxheimer reaction is the same as in the non-pregnant, circa 40%, based on small series.^{114,115} In addition, the pregnant woman may experience uterine contractions (circa 40–65%) which resolve within 24 h. The uterine contractions appear to occur secondary to the development of fever. Fetal heart rate

decelerations are also reported occurring in about 40%, concomitant with maternal fever, and resolve within 24 h of maternal penicillin treatment. In one series, no fetuses required delivery because of fetal heart rate abnormalities.¹¹⁵ Therefore, there may be a theoretical increased risk of spontaneous and iatrogenic pre-term delivery and foetal demise associated with the Jarisch-Herxheimer reaction, though these complications are also associated with maternal and fetal syphilis infection. Management of the Jarisch-Herxheimer reaction in pregnancy should be supportive as in the non-pregnant woman with antipyretics. There is no evidence that administration of high-dose oral prednisolone will reduce the occurrence of uterine contractions or fetal heart rate abnormalities.

- Maternal follow-up after treatment
 - It may take several months to observe a four-fold drop in RPR/VDRL titre and in many pregnancies labour will occur before these periods have elapsed. Moreover, women with late syphilis may have serofast RPR/VDRL titres. Hence, serological cure may not be demonstrable before birth of the neonate.

Recommendations

- All pregnant women should have syphilis serology at their first antenatal clinic visit, and if risk of syphilis is recognised re-screening later in pregnancy should be offered: 1A.
- When women have been cured of syphilis prior to pregnancy, and are not at risk of re-infection, the neonate will not require testing: 1B.
- Re-treatment in pregnancy is indicated where there is uncertainty of treatment or serologic cure is in doubt: 1B.
- When treatment of early syphilis is initiated in the third trimester, a second dose of benzathine one week after their first is recommended: 1B.
- For those allergic to penicillin, de-sensitisation should be considered. Where it is necessary to use macrolides to treat the mother during pregnancy, the neonate will require assessment and treatment at birth: 1C.
- Management should be in conjunction with fetal medicine and paediatric colleagues. Routine use of steroids to prevent the Jarisch-Herxheimer reaction is not recommended: 1C.
- Maternal diagnosis and treatment should be clearly communicated to the appropriate obstetrician, GP and paediatric team, with informed consent, a template birth plan is provided: 1C.

Table 3. Criteria to be applied (in Table 4) for diagnosing congenital syphilis.

Absolute	Major	Minor	Serology
<i>T. pallidum</i> identified on dark ground, PCR or histology	Condylomata lata	Fissures of lips	A. Positive RPR/VDRL or TPPA/TPHA
	Osteochondritis	Skin rash	B. Positive IgM
	Periosteitis	Mucous patches	C. Negative RPR/VDRL or TPPA/TPHA
	Snuffles (haemorrhagic rhinitis)	Hepatomegaly	D. Positive RPR/VDRL not becoming negative within four months
		Splenomegaly	E. Rising RLR/VDRL over three months
		Generalised lymphadenopathy	
		Neurological signs	
		Haemolytic anaemia	
		CSF pleocytosis or raised protein	

RPR: rapid plasma reagin; VDRL: Venereal Diseases Research Laboratory; CSF: cerebrospinal fluid; TPHA: *Treponema pallidum* haemagglutination assay; TPPA: *Treponema pallidum* particle agglutination assay; PCR: polymerase chain reaction.

Management of infants born to mothers with syphilis

- CS is uncommon in the UK, with approximately 10 cases reported annually. Consequently, most paediatricians will have little or no experience of managing the condition. The diagnosis of CS can be very difficult: most infected neonates appear normal at birth and passive transfer of maternal IgG across the placenta may cause reactive neonatal syphilis serology, even in the absence of CS. Given these difficulties, it is important that paediatricians and GU physicians work closely when managing neonates.
- The clinical signs of CS include:
 - Jaundice, anaemia, generalised lymphadenopathy, hepatosplenomegaly, non-immune hydrops, pyrexia, failure to move an extremity (pseudoparalysis of Parrot), low birth weight.
 - Skin rash (usually maculo-papular, but almost any form of rash is possible); the palms and soles may be red, mottled and swollen. Vesicles or bullae may be present.
 - Condylomata lata (flat, wart-like plaques in moist areas such as the perineum).
 - Osteochondritis, periosteitis (elbows, knees, wrists).
 - Ulceration of the nasal mucosa, rhinitis ('snuffles' usually presents after the first week of life).
- In order to make the diagnosis of CS more specific, Kaufman et al.¹¹⁶ listed a combination of clinical signs and laboratory tests; these are described in Tables 3 and 4. PCR testing for *T. pallidum* became available many years after publication of Kaufman's article and is added as an absolute

diagnostic criterion. Stillbirths were notably absent from the Kaufman criteria, resulting in a decreased sensitivity of CS diagnosis at the expense of specificity.

- A template syphilis birth plan has been developed to supplement the use of this guideline and support the appropriate management of babies born to mothers with positive syphilis serology, and is an appendix to this guideline.

Neonatal syphilis serology tests

- All children born to mothers with positive treponemal serology require clinical evaluation and syphilis serology tests, with the following exceptions:
 - Maternal biological false-positive serology.
 - Maternal syphilis cured prior to this pregnancy.
- Passively transferred maternal non-treponemal antibodies should decline by three and be negative by six months of age, and treponemal antibodies by 18 months of age.³
- Infants born to mothers diagnosed and/or treated for syphilis during the present pregnancy require RPR/VDRL and IgM tests at birth and at three months of age, then three monthly until negative. If these titres remain stable or increase, the child should be evaluated and treated for CS.³
- In the case of:
 - Infants with suspected congenital syphilis.
 - Infants born to mothers treated less than four weeks prior to delivery.
 - Infants of mothers treated with non-penicillin regimens.
 - Infants born to untreated mothers.

Table 4. Certainty of a congenital syphilis diagnosis from assessment of the infant using the clinical criteria in Table 2a.

Definite	Probable	Possible	Unlikely
One or more absolute criterion	Serology E or D One major criterion plus serology A or B Two or more minor criteria plus serology A or B One major and one minor criteria	Serology A or B with no clinical criteria	Serology C Serology A or B plus mother known to be adequately treated

- Infants born to mothers who were inadequately treated or who have no documentation of being treated.

Treatment for CS should be given using the regimen detailed below. Further investigations are indicated as detailed in the section above.

- For infants born to mothers treated with a penicillin-based regime more than four weeks prior to delivery with no evidence of re-infection or relapse, monitoring as detailed above is indicated.
- Untested older siblings should be screened for congenital syphilis.
- CS diagnosed in an older child or in adulthood should be managed as for late syphilis but the parents, all siblings and any sexual partner(s) should be screened for syphilis.

Recommendations

- Children born to mothers treated for syphilis in this pregnancy require clinical evaluation and syphilis screening serology: 1A.
- Syphilis serology should include non-treponemal titres and IgM at birth and three months, then three monthly until negative. Passively transferred maternal treponemal antibodies will be positive and unhelpful in this circumstance: 1B.
- Untested siblings should be screened for syphilis when a maternal or CS diagnosis is made: 1A.

Management in HIV-positive individuals

- Most experts and guidelines recommend the same treatment regimens/protocols as for HIV-uninfected individuals.^{3,43,101}
- HIV-infected individuals may be at higher risk of treatment failure compared to HIV-negative individuals; however, this risk is thought to be very small.

Prolonged treatment or additional antibiotic therapy has not been associated with significantly better outcomes.¹⁰¹

- Careful serologic follow-up is recommended, especially if non-penicillin regimens are used.
- Patients on effective ART may show improved clinical outcomes and reduced serologic failure rates.^{117–119}
- Subsequent increase in RPR/VDRL titres is most often linked to re-infection rather than treatment failure.
- The efficacy of non-penicillin regimens in HIV-positive patients has not been well studied. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin. Non-penicillin therapies should be used only in conjunction with close serologic and clinical follow-up.
- Limited clinical studies suggest that ceftriaxone might be effective.^{90,120,121} However, the optimal dose and duration of ceftriaxone therapy has not been defined.

Recommendation

- Testing and treatment for syphilis is the same HIV-positive individuals as those who are HIV negative: GRADE: 1B.

Recommended regimens (summarised in Table 5)

Potentially incubating syphilis/epidemiological treatment

1. Benzathine penicillin G 2.4 MU IM single dose: 1C.
2. Doxycycline 100 mg PO BD. × 14 days: 1C.
3. Azithromycin 2 g PO stat: 2C (See 'Caution re: macrolide therapy for syphilis' section).

Early syphilis (primary, secondary and early latent)

1. Benzathine penicillin G 2.4 MU IM single dose^{78,101}: 1B.

Alternative regimens

1. Procaine penicillin G 600,000 units IM daily × 10 days^{66,122–124}: 1C.
2. Doxycycline 100 mg PO BD × 14 days: 1C.
3. Ceftriaxone 500 mg IM daily × 10 days (if no anaphylaxis to penicillin): 1C.
4. Amoxicillin 500 mg PO QDS plus Probenecid 500 mg QDS × 14 days^{125,126}: 1C.
5. Azithromycin 2 g PO stat^{78,79} or Azithromycin 500 mg daily × 10 days: 2B. (See Caution re: macrolide therapy for syphilis' section)
6. Erythromycin 500 mg PO QDS × 14 days¹²⁷: 2B. (See Caution re: macrolide therapy for syphilis' section)

Late latent, cardiovascular and gummatous syphilis

1. Benzathine penicillin 2.4 MU IM weekly for three weeks (three doses): 1C.

Alternative regimens

1. Doxycycline 100 mg PO BD for 28 days¹²⁸: 2D.
2. Amoxicillin 2 g PO TDS plus probenecid 500 mg QDS for 28 days¹²⁹: 2C.
 - Steroids should be given with all anti-treponemal antibiotics for cardiovascular syphilis; 40–60 mg prednisolone OD for three days starting 24 h before the antibiotics.

Neurosyphilis including neurological/ophthalmic involvement in early syphilis

1. Procaine penicillin 1.8 MU–2.4 MU IM OD plus probenecid 500 mg PO QDS for 14 days^{3,99}: 1C.
2. Benzylpenicillin 10.8–14.4 g daily, given as 1.8–2.4 g IV every 4 h for 14 days: 1C.

Alternative regimens

1. Doxycycline 200 mg PO BD for 28 days¹²⁸: 2D.

2. Amoxicillin 2 g PO TDS plus probenecid 500 mg PO QDS for 28 days¹²⁹: 2D.
3. Ceftriaxone 2 g IM or IV for 10–14 days^{3,84–86,90,130,131}: 2D.
 - Steroids should be given with all anti-treponemal antibiotics for neurosyphilis; 40–60 mg prednisolone OD for three days starting 24 h before the antibiotics.

Early syphilis in pregnancy

- Trimesters one and two (up to and including 27⁺⁶ weeks):
- Benzathine penicillin G 2.4 MU IM. Single dose: 1B.
- Trimester three (from week 28 to term):
- Benzathine penicillin G 2.4 MU IM, on days 1 and 8: 1B.

Alternative treatments (all three trimesters)

1. Procaine penicillin G 600,000 unit IM. Daily for 10 days: 1C.
2. Amoxicillin 500 mg PO q.d.s. plus probenecid 500 mg PO q.d.s for 14 days: 2C.
3. Ceftriaxone 500 mg IM daily for 10 days: 2C.
4. Erythromycin 500 mg PO q.d.s for 14 days: 2C (see Caution re: macrolide therapy for syphilis' section)
5. Azithromycin 500 mg PO daily for 10 days: 2C (see 'Caution re: macrolide therapy for syphilis' section)

Late syphilis in pregnancy

- Late latent, cardiovascular and gummatous syphilis (all three trimesters):
- 1. Benzathine penicillin G 2.4 MU IM weekly on days 1, 8 and 15 (three doses): 1C.
- Steroids should be given with all anti-treponemal antibiotics for cardiovascular syphilis; 40–60 mg prednisolone OD for three days starting 24 h before the antibiotics.

Alternative treatment

1. Procaine penicillin G 600,000 units IM OD for 14 days: 1C.
2. Amoxicillin 2 g PO t.d.s. plus probenecid 500 mg q.d.s for 28 days: 2C.

Table 5. Recommended treatment regimens.

Clinical stage	Recommended regimens	Alternative regimen	Clinical notes
Incubating syphilis/epidemiological treatment	<ol style="list-style-type: none"> 1. Benzathine penicillin 2.4 MU IM single dose 2. Doxycycline 100 mg PO BD × 14 days 3. Azithromycin 2 g PO stat 		Resistance limits the use of macrolide antibiotics and they should be used as a last resort only when follow-up can be assured.
Early (primary/secondary/early latent) syphilis	<ol style="list-style-type: none"> 1. Benzathine penicillin 2.4 MU IM single dose 	<ol style="list-style-type: none"> 1. Procaine penicillin G 600 000 units IM daily × 10 days 2. Doxycycline 100 mg PO BD × 14 days 3. Ceftriaxone 500 mg IM daily × 10 days 4. Amoxicillin 500 mg PO QDS plus Probenecid 500 mg × 14 days 5. Azithromycin 2 g PO stat or Azithromycin 500 mg daily × 10 days 6. Erythromycin 500 mg PO QDS × 14 days 	Resistance limits the use of macrolide antibiotics and they should be used as a last resort only when follow-up can be assured.
Late latent, cardiovascular and gummatous syphilis	<ol style="list-style-type: none"> 1. Benzathine penicillin 2.4 MU IM weekly for three weeks (three doses) 	<ol style="list-style-type: none"> 1. Procaine penicillin 600,000 units IM OD for 14 days 2. Doxycycline 100 mg PO BD for 28 days 3. Amoxicillin 2 g PO TDS plus probenecid 500 mg QDS for 28 days 	Steroids should be given with all anti-treponemal antibiotics for cardiovascular and neurological syphilis; 40–60 mg prednisolone OD for 3 days starting 24 h before the antibiotics.
Neurosyphilis	<ol style="list-style-type: none"> 1. Procaine penicillin 1.8 MU-2.4 MU IM OD plus probenecid 500 mg PO QDS for 14 days 2. Benzylpenicillin 10.8–14.4 g daily, given as 1.8–2.4 g IV every 4 h for 14 days: IC. 	<ol style="list-style-type: none"> 1. Doxycycline 200 mgs PO BD for 28 days 2. Amoxicillin 2 gm PO TDS plus probenecid 500 mg PO QDS for 28 days 3. Ceftriaxone 2 g IM or IV OD for 10–14 days 	
Treatment of early syphilis in pregnancy	<ol style="list-style-type: none"> 1. Benzathine penicillin 2.4 MU IM single dose in the first and second trimesters. When maternal treatment is initiated in the third trimester, a second dose of benzathine penicillin 2.4 MU IM should be given after one week (day 8). 	<ol style="list-style-type: none"> 1. Procaine penicillin G 600,000 unit IM daily × 10 days 2. Amoxicillin 500 mg PO QDS plus probenecid 500 mg PO QDS × 14 days 3. Ceftriaxone 500 mg IM daily × 10 days 4. Erythromycin 500 mg PO qds × 14 days OR Azithromycin 500 mg PO daily × 10 days plus evaluation and treatment of neonates at birth with penicillin 	Management should be in close liaison with obstetric, midwifery and paediatric colleagues.
Treatment of late syphilis in pregnancy	Manage as in non-pregnant patient (doxycycline contraindicated)		
Syphilis treatment in HIV-positive individuals	Treatment as appropriate for the stage of infection		
Congenital syphilis			

(continued)

Table 5. Continued.

Clinical stage	Recommended regimens	Alternative regimen	Clinical notes
	1. Benzyl penicillin sodium - 60–90 mg/kg daily IV (in divided doses given as –30 mg/kg 12 hourly in the first 7 days of life and 8 hourly thereafter for 10 days: 1C	2. Procaine penicillin 50,000 u/kg daily IM × 10 days	In children IV therapy (option one here) is preferable due to the pain associated with IM injections.

Neurosyphilis in pregnancy

1. Procaine penicillin G 1.8–2.4 MU IM o.d. plus probenecid 500 mg PO q.d.s. for 14 days³: 1C 2010.
2. Benzylpenicillin 10.8–14.4 g daily, given as 1.8–2.4 g IV every 4 h for 14 days: 1C.

Alternative regimens

1. Amoxicillin 2 g PO t.d.s. plus probenecid 500 mg PO q.d.s. for 28 days: 2D.
2. Ceftriaxone 2 g IM (with lidocaine as diluent) or IV (with water for injections as diluent, NOT Lidocaine) for 10–14 days (if no anaphylaxis to penicillin): 2D.
3. Steroids should be given with all anti-treponemal antibiotics for neurosyphilis; 40–60 mg prednisolone OD for three days starting 24 h before the antibiotics.

Syphilis in HIV-positive individuals

- Treatment as appropriate for the stage of infection; HIV-positive individuals to be given the same treatment regimens as HIV-negative individuals: 1B.

Congenital syphilis

1. Benzyl penicillin sodium 60–90 mg/kg daily IV (in divided doses given as – 30 mg/kg 12 hourly in the first seven days of life and 8 hourly thereafter for 10 days: 1C.

Alternative regimen

1. Procaine penicillin 50,000 μ /kg daily IM × 10 days.

In children, IV therapy (option one here) is preferable due to the pain associated with IM injections: 1C.

Caution re: Macrolide therapy for syphilis

- Macrolide antibiotics are to be used if only option available and when follow-up can be assured: 1B.
- Where it has been necessary to use macrolides to treat the mother during pregnancy, the neonate will require assessment and treatment at birth: 1A.

Interruptions in treatment for late and congenital syphilis

- If drug administration is interrupted for more than one day at any point during the treatment course, it is recommended that the entire course is restarted¹³²: 1D.

Preparation of intramuscular penicillin injections

- Both intramuscular benzathine penicillin and procaine penicillin infections are more tolerable to the patient if diluted with lidocaine as per the protocol in the appendix (*Farmaproina powder and solvent for suspension for injection, Reig Jofre Group*),¹³³ so this preparation is recommended: 1D.

Reactions to treatment

- Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area. All patients should be kept on clinic premises for 15 minutes after receiving their first injection to observe for immediate adverse reactions. In addition, patients should be advised to seek urgent medical attention if they experience symptoms or signs of an allergic reaction: shortness of breath, itchy wheals on their skin, facial swelling or tightness in their chest or throat.

- Jarisch-Herxheimer reaction: An acute febrile illness with headache, myalgia, chills and rigours which resolves within 24 hours. This is common in early syphilis and is usually not clinically significant unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress. Management should include advice to use antipyretics if it occurs and reassurance. It is uncommon in late syphilis but can potentially be life threatening if there is involvement of critical sites (e.g. coronary ostia, larynx and nervous system). There is no evidence that the use of steroids prevents these serious consequences; however, there is evidence in early syphilis that steroids prevent the fever associated with the Jarisch-Herxheimer reaction.¹³⁴ This suggests a biological plausibility that steroids may also prevent the wider complications of the reaction. Furthermore, severe clinical deterioration in early syphilis with optic neuritis and uveitis has been reported following treatment and, as steroids are also used in the management of these conditions unrelated to syphilis, biological plausibility would suggest that they may help. The recommended dose is prednisolone 40–60 mg daily for three days started 24 h before the anti-treponemal antibiotics.
 - Procaine reaction (procaine psychosis, procaine mania, Hoigne's syndrome): This is due to inadvertent intravenous injection of procaine penicillin. It is characterised by fear of impending death and may cause hallucinations or fits immediately after injection and lasts less than 20 minutes. Calm and verbal reassurance is required and restraint may be necessary. Management of seizures is as per local practice.
 - Anaphylactic shock: Facilities for the treatment of anaphylaxis should be available. Standard treatment protocols for the management of anaphylactic shock should be followed.
 - Allergy: Penicillin desensitisation should be considered for patients reporting a history of penicillin allergy.^{113,135}
 - Many people reporting penicillin allergy will not display hypersensitivity on re-exposure to penicillin either because the hypersensitivity has resolved or they were never allergic to penicillin. A careful history may help to identify the latter group. Skin testing to confirm allergy should precede desensitisation. Skin testing and desensitisation do carry risks of anaphylaxis and should be carried out with immediate access to resuscitation equipment and expertise.
- therapy, observe for immediate reactions to treatment: 1C.
- Steroid therapy is recommended when managing neurological (both early and tertiary) or cardiovascular syphilis to prevent potentially serious consequences of the Jarisch-Herxheimer reaction; 40–60 mg OD for three days starting 24 h before anti-treponemal antibiotics: 1D.
 - Consider skin testing and subsequent penicillin desensitisation and treatment for those reporting allergy: 2A.

Management of sexual partners

- All patients with a diagnosis of syphilis should have partner notification (PN) discussed at the time of diagnosis by a trained healthcare professional. Where the outcome is not resolved at initial interview, there should be documented attempts to re-interview the patient in order to offer further support and gain further information in order to verify outcomes.
- For patients with primary syphilis, sexual partners within the last three months should be notified as the incubation period is up to 90 days. PN may have to extend to two years for patients with secondary syphilis, with clinical relapse or in early latent syphilis. Of contactable sexual partners of patients and pregnant women with early syphilis 46–60% will also have the infection.⁶ For MSM, many sexual contacts are met in anonymous sex venues, e.g. saunas, internet or cruising grounds, which can make PN difficult. Service links with high-risk venues to provide screening and advice may prove useful.
- Individuals who are sexual contacts but are asymptomatic of early syphilis should be offered either epidemiological treatment or re-screening for syphilis 12 weeks after their last exposure.
- In latent syphilis, strenuous attempts should be made to locate any previous serology or documented treatment which would aid disease staging. This should then inform PN activities. Individuals with late latent syphilis are usually unable to transmit the infection to sexual partners. Although vertical transmission may occur many years of initial infection, this becomes unusual as time progresses and after the stages of early syphilis. Unless the time-frame during which infection occurred can be determined, it is reasonable for sexual partners and children born to women diagnosed with late latent syphilis of unknown duration to undergo screening.
- All patients should be offered patient and provider referral as a method of contacting any sexual

Recommendations

- Advise patients of possible or common reactions to treatment and after administering parenteral

partners. Use of electronic means of contact should also be considered, e.g. profiles on dating websites, etc. The method agreed upon with the patient should be clearly documented. See www.bashh.org/guidelines for PN statement.

Recommendations

- All patients should have PN discussed at diagnosis with re-interview if required. The look-back period is as appropriate for their stage of syphilis: 1B.
- Epidemiologic treatment should be offered for asymptomatic contacts in the window period: 1B.

Follow-up

- Follow-up is in order to detect possible re-infection and relapse.
- It may take a number of months for the non-treponemal titres to drop four-fold following treatment, particularly following treatment of re-infections.
- Recommended clinical and serological (RPR or VDRL) follow-up is at three, six and 12 months, then if indicated, six monthly until VDRL/RPR negative or serofast.
- A sustained four-fold or greater increase in the VDRL or RPR titre suggests re-infection or treatment failure. Treatment failure is characterised by:
 - Four-fold or greater increase in non-treponemal test titre.
 - Recurrence of signs or symptoms.
 - Re-infection excluded.
- CSF examination and re-treatment are indicated for individuals whose non-treponemal test titres do not decrease four-fold within 12 months of therapy. If CSF examination is normal, re-treatment should be with benzathine penicillin G administered as three doses of 2.4 million units IM each at weekly intervals.³ Specific treponemal tests may remain positive for life following effective treatment; clear documentation is necessary to prevent unnecessary re-treatment, and patient given this as written information.
- Re-infection or relapse should be re-treated preferably with supervised treatment schedules to ensure compliance, and sexual partners should be screened and offered epidemiological treatment.
- In those with concomitant HIV infection, initial follow-up is as detailed above. Lifelong annual monitoring with syphilis serology is recommended and in outbreak situations six monthly (coinciding with HIV follow-up visits).

Recommendations

- Minimal recommended follow-up is syphilis serology at three, six and 12 months, or until serofast: 1D.

Auditable outcome measures

- The percentage of confirmed syphilis cases having a record of a RPR or VDRL titre obtained pre-treatment (standard 97% confirmed syphilis cases).
- The percentage of confirmed syphilis cases having fully adhered to a recommended treatment (standard 97% confirmed syphilis cases).
- The percentage of cases having the outcome of (an) agreed contact action(s), or the decision not to contact, documented for all contacts, within the appropriate look back interval (see <http://www.bashh.org/documents/2012%20Partner%20Notification%20Statement.pdf>) (standard 97% confirmed syphilis cases).
- The ratio of contacts per index case of confirmed syphilis, with contact attendance at a Level 1, 2 or 3 sexual health service documented as (a) reported by the index case or (b) confirmed by a healthcare worker, within four weeks of the date of the first PN discussion (standard (a) 0.6 and (b) 0.4 contact per index case within an agreed audit interval).
- The percentage of confirmed syphilis cases having a record of a RPR or VDRL titre obtained six months post-treatment (standard 65% confirmed syphilis cases).

Acknowledgements

The authors thank Dr P McMaster, Consultant in Paediatric Infectious Diseases, North Manchester General Hospital, for his contribution to the birth plan. The following Genitourinary medicine physicians piloted the final guideline in their clinics: Dr Rajesh Hebrom, Dr Vinod Kumar, Dr Harriet Wallace, Dr Janet Wilson, Dr Melinda Tenant-Flowers, Dr Mike Brady, Dr Rachel Jackson and Dr Ben Gorney.

Declaration of conflicting interests

All authors have signed the BASHH CEG COI form, indicating no conflict of interest.

Funding

This guideline was commissioned and edited by the CEG of the BASHH, without external funding being sought or obtained.

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Appendix I. Administration of Procaine and Benzathine Penicillin Preparations

Administration

To reduce the pain experienced by patients receiving benzathine and procaine penicillin injections, 1% lidocaine (lignocaine) can be used as an alternative diluent to water for injections (unlicensed indication) (133).

Benzathine

Dose: 2.4 Mega units IM weekly for up to 3 weeks.

Presentation: Powder for suspension for injection.

Reconstitute the vial with 8 ml of 1% lidocaine hydrochloride BP solution. Split the resultant suspension into two equal volumes.

The suspension should be administered by deep intramuscular injection in two different sites.

Administration

1. Add solvent to vial and turn the vial gently whilst warming it in your hands.
2. Extract the suspension with a needle different from the one you will use for injection.
3. To inject, stick an 'empty' 0.9 calibre needle into the patient.
4. Place the syringe and aspirate to check that no blood comes out.
5. Inject.

Procaine

Dose: 1.8–2.4 mega units IM daily for 14 days.

Presentations: Powder for suspension for injection.

Reconstitute two 1.2 mega unit vials with 4 ml of 1% lidocaine hydrochloride BP solution each. The required volume should be administered by deep intramuscular injection into two different sites.

Solutions in lidocaine **MUST NOT** be administered intravenously.

Inadvertant intravenous administration of lidocaine can cause bradycardia (which may lead to cardiac arrest), fitting and/or sedation. Use the 'aspiration technique' of injection to minimise the risk of this happening.

Contraindications

- Allergy to penicillin or lignocaine.
- Concomitant anticoagulant therapy.
- Bleeding diathesis (e.g. Haemophilia).

Precautions

For patients with penicillin allergy, cross reactivity to other beta-lactams such as cephalosporins should be taken into account.

Appendix 2. Syphilis birth plan

Maternal details

Estimated date of delivery. Maternal syphilis diagnosis, treatment details and dates:

Other concerns (e.g. Re-infection risk from partner, treatment late in pregnancy, etc):

GUM advice for infant management

1. Mother adequately treated prior to this pregnancy with no risk of congenital syphilis.
At birth: Infant requires no additional physical examination or tests for syphilis.
Follow-up: Infant needs no follow-up for syphilis.
2. Mother treated for syphilis during this pregnancy with low risk of congenital syphilis.
At birth: Assess infant for signs of congenital syphilis. If no concerns perform routine syphilis screening on infant venous (not cord) serum sample, request 'Syphilis screen + RPR + treponemal IgM'.

Follow-up: Request 'Syphilis screen + RPR + treponemal IgM' and repeat at three months of age in all babies then every three months until RPR is negative (this usually occurs by six months).

If clinical signs suggest CS (see 2015 BASHH guideline), manage according to 'option 3' below.

3. There is a significant risk of congenital syphilis.

At birth: Assess infant for signs of CS (see 2015 BASHH guideline). Request 'Syphilis screen + RPR + treponemal IgM' plus FBC, U&E, LFT, ALT. Lumbar puncture (request WBC, protein, RPR, TPPA) and further tests as clinically indicated; long bone and chest X-rays, ophthalmology and audiology reviews and (if available) samples from lesions for dark ground microscopy and PCR for *T. pallidum*.

Treatment for congenital syphilis: Benzyl penicillin sodium – 60–90 mg/kg daily IV (in divided doses given as – 30 mg/kg 12 hourly in the first seven days of life and 8 hourly thereafter for 10 days)

Follow-up months 1 and 3: Request 'syphilis screen + RPR + treponemal IgM'.

Follow-up months 6 and 12: Request RPR only. Discharge infant when RPR titre has dropped at least fourfold (e.g. from 1 in 32 to 1 in 8) or becomes negative.

Please discuss all infants with suspected syphilis or requiring treatment with the GUM team on call or any blood tests requiring interpretation.

Local contact details:

Plan completed by:

Date:

Copies to: obstetric team, GP, paediatric/neonatal team

Appendix 3. Equality impact assessment

Topic suggestion: impact assessment				
Guidance title: BASHH Guidelines for the Management of Syphilis 2014. Completed by: Margaret Kingston. Date: 20 July 2014				
How relevant is the topic to equality?	Inequalities in health impact of the condition or public health issue	Potential of guidance to add value	Priority for NHS or other government department	Topic relevance: conclusions and outcomes
	<ul style="list-style-type: none"> Prevalence and impact of condition or public health problem Prevalence of risk factors 	<ul style="list-style-type: none"> Inequalities in access, uptake or impact Timeliness Equality issues identified by proposers of the topic Equality issues identified by patient or lay organisations 	<ul style="list-style-type: none"> Department of Health DCLG, DCSF, DoT, Home Office, etc. Other agency or ALB 	<ul style="list-style-type: none"> High/medium/low/none Not known/inconclusive Reasons for rating Recommendation
	<p>The infection presently disproportionately affects gay men.</p> <p>Women screened in antenatal clinic and a significant section of the guideline addresses the specific issues concerned with management of women during pregnancy and their infants.</p>	<p>Clarity of management in pregnancy and diagnosing and managing of syphilis in infants (a rare condition where guidance is needed) is needed. A template birth plan will be hoped to enhance communication between the team managing pregnancy and the. Following the changes in this guideline many babies will not require testing for syphilis; a major improvement.</p>	<p>Implementation for pregnant women and babies will improve communication within the team and reduce infant testing. Clarity on further investigations/examination required should streamline some consultations.</p>	<p>Impact on care of gay men and women and their children.</p>
Gender	<ul style="list-style-type: none"> Women Men 			
Race	<p>Most gay men affected are white.</p> <p>Many women affected and their families are from eastern Europe, Africa, Asia or the Caribbean.</p>	<p>As above</p>	<p>As above</p>	<p>Some improved streamlining of care for pregnant women from ethnic minorities with positive treponemal serology and their families.</p>
<ul style="list-style-type: none"> Asian or Asian British Black or black British People of mixed race Irish White British Chinese Other minority groups not listed 				
Disability	<p>Some patients treated may be in these groups and their risk of sexual exploitation should be</p>	<p>All cases of syphilis should be managed by GU Physicians; therefore all cases should</p>	<p>Safeguarding concerns should be addressed.</p>	<p>Consideration of patients in these groups being at risk of sexual exploitation/abuse</p>
<ul style="list-style-type: none"> Sensory Learning disability 				

(continued)

Continued.

Topic suggestion: impact assessment			
Guidance title: BASHH Guidelines for the Management of Syphilis 2014. Completed by: Margaret Kingston. Date: 20 July 2014			
How relevant is the topic to equality?	Inequalities in health impact of the condition or public health issue	Potential of guidance to add value	Priority for NHS or other government department
	<p>Inequalities in health impact of the condition or public health issue</p> <ul style="list-style-type: none"> • Mental health • Cognitive • Mobility • Other impairment 	<p>have safeguarding concerns addressed by their departmental policies. GU physicians receive level 3 safeguarding training.</p> <p>Addressing these issues if specifically covered in the guideline.</p>	<p>Topic relevance: conclusions and outcomes</p> <p>should be made as part of GUM departments safeguarding training.</p>
	<p>Young adults are mainly affected with impact of the diagnosis on their sexual partners, children and possibly siblings. Syphilis is children is rare and specific guidance is given to managing this.</p>	<p>Management of young adults and children specifically addressed.</p>	
	<p>Gay men disproportionately affected with impact on their sexual relationships.</p>	<p>Clear guidance for notifying partners.</p>	<p>Importance of the role of health advisors.</p> <p>Specific partner notification and follow-up guidance.</p>
	<p>People from these groups, particularly identified via antenatal screening of women in these communities, are disproportionately affected.</p>	<p>Expansion of the management in pregnancy, management of children and simplifying testing of children and the birth plan to support sharing of information within the health-care team will help address issues in this group.</p>	<p>Value of the pregnancy multidisciplinary team and collaborative working with GUM departments.</p> <p>Team working crucial. Inclusion of syphilis birth plan should facilitate this.</p>
	<p>Sexual orientation and gender identity</p> <ul style="list-style-type: none"> • Lesbians • Gay men • Bisexual people • Transgender people <p>Religion/belief</p> <p>Socio-economic status</p> <p>Other categories</p> <ul style="list-style-type: none"> • Gypsy travellers • Refugees and asylum seekers • Migrant workers • Looked after children • Homeless people 		