UK National Guidelines on the Management of Syphilis 2008

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SCOPE AND PURPOSE

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications 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, presenting to health-care professionals, working in departments offering level 3 care in STI management (see national strategy)[1] within the United Kingdom. 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.

STAKEHOLDER INVOLVEMENT

The document was reviewed by the Clinical Effectiveness Group of British Association for Sexual Health and HIV (BASHH), and their comments incorporated. The draft guideline was placed on the BASHH website and any comments received after three months were reviewed by the authors and acted on appropriately.

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New in the 2008 guidelines

- New guideline format: A single guideline covering screening and investigations for syphilis, clinical features, management and follow-up for all stages of infections: early, late, congenital, in pregnancy and in HIV-positive individuals.
- When evaluating possible neurological involvement a lumbar puncture is indicated in those with neurological symptoms/signs or those who have failed therapy and consideration should be given to neurological imaging first. A section on interpretation of the cerebrospinal fluid (CSF) results is included.
- When managing syphilis infection in pregnancy, referral to fetal medicine consultant for evaluation of fetal involvement and monitoring for fetal distress during treatment is recommended after 26 weeks gestation.
- Changes to treatment regimens:
  - Early syphilis:
    - Benzathine penicillin G single dose first-line therapy
    - Azithromycin single dose as a second-line alternative therapy: caution; reports of intrinsic macrolide resistance
  - Late syphilis:
    - Benzathine penicillin G three weekly doses first-line therapy (except for neurosyphilis: procaine penicillin G with concomitant oral probenecid remains first-line therapy for this)
  - Pregnancy:
    - First and second trimesters: give benzathine penicillin G, single dose. However, when maternal treatment is initiated in the third trimester, a second dose of benzathine penicillin G to be given one week after the first.
    - Ceftriaxone 500 mg i.m. × 10 days added to alternatives
    - Late: As in non-pregnant patients (avoid tetracyclines)
  - Infants:
    - Guidance for screening and treatment for babies born to mothers with syphilis

  - HIV-positive patients: Treat as appropriate for stage of infection, that is, HIV-positive patients are treated with the same regimens as HIV-negative patients
- Management of sexual partners: Recognition that partner notification may be difficult in context of current syphilis outbreaks and achieving 60% partner notification rates is not always possible and screening in high-risk venues may be appropriate.
- Auditable outcomes: Measuring rapid plasma reagin test (RPR)/Venereal Diseases Research Laboratory (VDRL) at commencement of therapy introduced as an auditable outcome.
- Appendices:
  - Reference to sources of procaine penicillin G
  - Use of lidocaine as diluent for Benzathine penicillin G

INTRODUCTION AND METHODOLOGY

The objective of this guideline is to facilitate the appropriate investigation and management of individuals with all stages of syphilis. This guideline has been developed by a group (see membership of the guideline revision group for details) who have reviewed the previous published guidelines for the management of early and late syphilis[2,3] together with more recent clinical data in order to produce this updated, unified guideline. Recommendations made are graded as stated in the BASHH guideline specifications[4] as level of evidence (Ia-V) and grade of recommendations (A–C).

AETIOLOGY

Syphilis is caused by infection with the spirochete bacterium *Treponema pallidum subsp pallidum*. This is transmitted from one person to another either by direct contact with an infectious lesion (usually occurring during sexual contact), during pregnancy from mother to child or via infected blood products.

CLASSIFICATION

Syphilis is classified as acquired or congenital. Acquired syphilis is divided into early (primary, secondary and early latent <2 years of infection) and late (late latent >2 years of infection, tertiary including gummatous, cardiovascular and neurological) syphilis. Congenital syphilis is divided into early (diagnosed in the first two years of life) and late (presenting after two years).

CLINICAL FEATURES[5–7]

- Primary syphilis is characterized by an ulcer (the chancre) and regional lymphadenopathy. The chancre is classically in the anogenital region, is single, painless and indurated with a clean base discharging clear serum. However, chancres may be multiple, painful, purulent, destructive, extragenital (most frequently oral) and may cause the syphilitic balanitis of Follman.[8] There may also be mixed aetiology.[9] Any anogenital ulcer should be considered to be due to syphilis unless proven otherwise.
- Secondary syphilis is characterized by multisystem involvement within the first two years of infection. There is often a rash (typically generalized macular, papular or macular–papular often affecting the palms and soles), condylomata lata, mucocutaneous lesions, generalized lymphadenopathy and less commonly: patchy alopecia, anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periosteitis and glomerulonephritis.[10–15] The rash is classically non-itchy but may be itchy, particularly in dark-skinned patients.[16]
- Latent syphilis is *T. pallidum* infection diagnosed on serological testing with no symptoms or signs. Within the first two years of infection this is early latent syphilis and beyond that late latent syphilis.
- Symptomatic late syphilis can be categorized into neurosyphilis, cardiovascular syphilis and gummatous syphilis, and these may coexist. Tertiary syphilis is a term often used synonymously with late symptomatic syphilis but generally excludes meningovascular syphilis. A large prospective cohort study of untreated patients with *T. pallidum* infection in the pre-antibiotic era demonstrated that symptomatic late syphilis may develop in approximately one third of individuals.[17] The clinical features of symptomatic late syphilis are summarized in table one.
- Congenital syphilis[5,18,19]
  - Early; includes a rash, condylomata lata, vesiculobullous lesions, snuffles, haemorrhagic rhinitis, osteochondritis, periostitis, pseudoparalysis, mucous patches, perioral fissures, hepatosplenomegaly, generalized lymphadenopathy, non-immune hydrops, glomerulonephritis, neurological or ocular involvement, haemolysis and thrombocytopenia.
  - Late; including stigmata: Interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddlenose deformity, sterno-clavicular thickening, paroxysmal cold haemoglobinuria, neurological or gummatous involvement.

DIAGNOSIS

History and examination

- Symptoms of early syphilis
- Details of previous treatment (place of treatment, diagnosis made, treatment given, RPR/VDRL titre at discharge)
- Obstetric history, potential complications of syphilis e.g. miscarriages, stillbirths
- Blood donation and antenatal screening history
- Other treponemal infections; yaws, pinta and a history of living in countries where these conditions are endemic
- In early infection examination of the genitals, skin, mucosal surfaces and lymph nodes for signs of primary and secondary syphilis.
- In late and congenital syphilis a thorough clinical examination should be undertaken for the clinical manifestations of syphilis. This should include a full systems review including skin and mucosal surfaces, lymph nodes, cardiovascular and neurological systems.

DEMONSTRATION OF *T. PALLIDUM* FROM LESIONS OR INFECTED LYMPH NODES

- Dark ground microscopy[20] (III, B)
  - Should be performed by experienced observers.

- If the initial test is negative repeat daily for three days.
- Less reliable in examining rectal and non-penile genital lesions and not suitable for examining oral lesions due to commensal treponemes.

- Polymerase chain reaction (PCR)[21–23] (IIb, B)
  - May be used on oral or other lesions where contamination with commensal treponemes is likely.
  - Available at the Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency, Colindale, London, at the Clinical Virology Laboratory, Manchester Royal Infirmary and for Scotland at the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory.
  - Due to limited availability and the time taken to obtain a result this is not a replacement for dark field microscopy in the clinic setting.
  - In certain circumstances PCR may be helpful in diagnosis by demonstrating *T. pallidum* in tissue samples, vitreous fluid and CSF.[24–27]

Serological test for syphilis: (II, B)

- These should be routinely performed in genitourinary medicine clinic attendees.
- Specific (treponemal) tests: treponemal enzyme immunoassay (EIA) to detect immunoglobulin G (IgG), IgG and immunoglobulin M (IgM) or IgM, *T. pallidum* chemiluminescent assay,[28–30] *T. pallidum* haemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorbed test (FTA-abs), *T. pallidum* recombinant antigen line immunoassay.
  - Request EIA for antitreponemal IgM if primary syphilis is suspected (European Syphilis Guideline IUSTI/WHO, 2007, in final preparation);[31–33] IgM is detectable towards the end of the second week of infection while IgG is detectable usually in the fourth or fifth week.
  - All the specific tests are almost invariably positive in secondary and early latent syphilis (a delayed serological response may occur in secondary infection but this is rare, even in the presence of HIV).[34–36]
- Cardiolipin (non-treponemal) tests: VDRL carbon antigen test/RPR.
  - A quantitative VDRL/RPR should be performed when treponemal tests indicate syphilis (European Syphilis Guideline IUSTI/WHO, 2007, in final preparation) as this helps stage the disease and indicates the need for treatment.
  - A false-negative cardiolipin (reagin) test may occur in secondary or early latent syphilis due to the prozone phenomenon when testing undiluted serum.[37] This may be more likely to occur in HIV-infected individuals.[38]
  - A VDRL/RPR titre of >16 and/or a positive IgM test indicate active disease and the need for treatment,[39] although serology must be interpreted in the light of the treatment history and clinical findings.
- Recommended for screening: Treponemal EIA (preferably a test that detects both IgG and IgM) or TPPA or VDRL/RPR and TPHA and confirm a positive screening test with a different treponemal test (European Syphilis Guideline IUSTI/WHO, 2007, in final preparation).[32,33] An immunoblot (*Treponema pallidum* recombinant antigen line immunoassay)[40] is recommended when the standard confirmatory test does not confirm the positive treponemal screening test result (European Syphilis Guideline IUSTI/WHO, 2007, in final preparation). The FTA-abs is not recommended as a standard confirmatory test (European Syphilis Guideline IUSTI/WHO, 2007, in final preparation).
- Always repeat positive tests on a second specimen to confirm the result. (IV, C)
- A quantitative VDRL/RPR should be performed on a specimen taken on the day that treatment is started (IV, C) as this provides an accurate baseline for monitoring response to treatment.
- Repeat screening is recommended:
  - Three months after exposure in the case of a single 'high risk' exposure (unprotected oral, anal or vaginal intercourse with homosexual male multiple partners, anonymous partner in saunas and other venues, commercial sex worker, partner linked with a country where the prevalence of syphilis is known to be high).
  - Six weeks and at three months (including a specific IgM test) after presentation in those with dark field negative ulcerative lesions that could be due to syphilis or contacts of suspected or proven syphilis. (IV, C)
- The VDRL/RPR and EIA-IgM[27] are often negative in late syphilis but this does not exclude the need for treatment.
- Other treponemal infections such as Yaws or Pinta may give identical results although the RPR/VDRL is usually of low titre (<1:8). Because it is not possible to exclude latent syphilis in this situation, many clinicians manage patients who may have these infections as though they have syphilis. The rationale of this approach should be discussed with the patient.
- Rapid tests for syphilis are available[41] but their main role is likely to be in field conditions in developing countries and potentially in outreach work.

Evaluation of neurological, cardiovascular or ophthalmic involvement

- Chest X-ray (CXR) in late latent syphilis or if there are any signs of aortic disease. In pregnant women with late latent syphilis, a CXR is not routinely recommended unless cardiovascular signs or symptoms deem it is necessary.
- Neurological imaging should be considered in those with neurological symptoms or signs. Patients should have a thorough neurological examination to rule out focal neurology or papilloedema that may indicate raised intracranial pressure and a computed tomography of the head requested if these signs are present prior to lumbar puncture.
- There is continued debate around the necessity of CSF examination in asymptomatic patients. A study of risks and benefits of lumbar puncture in this group has suggested that it is not indicated[42] and a wide range of penicillin doses appear efficacious in preventing clinical progression of asymptomatic neurosyphilis.[43] 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[44] whereas a serum RPR $\geq$ 1:32 has been demonstrated to predict CSF abnormalities.[45] Indications for CSF examination in late syphilis infection include:
  - Neurological or ophthalmic signs or symptoms
  - Treatment failure

- Interpretation of CSF serology:
  - In order for these tests to be interpreted accurately, it is vital that the CSF should not be macroscopically contaminated with blood.[46]
  - 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^3).
  - Positive CSF VDRL and CSF TPPA tests should be repeated quantitatively.
  - The overall sensitivity of the CSF VDRL/RPR is around 50% with a range of 10% for asymptomatic cases to 90% for symptomatic cases;[47] a negative CSF VDRL/RPR does not exclude neurosyphilis and a positive CSF VDRL/RPR (in the absence of substantial contamination of CSF with blood) is diagnostic of neurosyphilis.[48]
  - A negative treponemal test on CSF excludes neurosyphilis and a positive test is highly sensitive for neurosyphilis but lacks specificity[49] because reactivity may be caused by transudation of immunoglobulins from the serum into the CSF or by leakage through a damaged blood brain barrier resulting from conditions other than syphilis. Neurosyphilis is unlikely when the CSF TPHA titre is <320 or the TPPA titre <640. The TPHA index (CSF TPHA/albumin quotient [CSF albumin $\times 10^3$/serum albumin]) allows for impaired barrier function and is more sensitive than the CSF VDRL while maintaining high specificity.[50,51] A TPHA index >70 and a CSF TPHA titre >320 are the most reliable in supporting a diagnosis of neurosyphilis[50] but unfortunately determination of the TPHA index is not widely available.

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[142] yet this does not become clinically significant in the majority of patients.[17]
Meningovascular	2–7 years	Focal arteritis inducing infarction/meningeal inflammation; signs dependent on site of vascular insult. Occasional prodrome; headache, emotional lability, insomnia.
Parenchymatous		
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; lightening pains, areflexia, paraesthesia, sensory ataxia, Charcot's joints, mal perforans, optic atrophy, pupillary changes (e.g. Argyll Robertson pupil).
Cardiovascular	10–30 years	Aortitis (ascending usually); 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.

Diagnosis of cardiovascular syphilis

This diagnosis is made by the presence of the typical clinical features of cardiovascular syphilis (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.

Diagnosis of congenital syphilis

- Direct demonstration of *T. pallidum* by dark ground microscopy and/or PCR of exudates from suspicious lesions, or body fluids, e.g. nasal discharge.[52,53]
- 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 VDRL/RPR 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.
  - If the IgM test is negative, the other tests are reactive with titres less than four-fold higher than those of the mother and there are no signs of congenital syphilis, then repeat reactive tests at three, six and 12 months of age or until all tests become negative (usually by six months). Also repeat the IgM at three months in case the infant's response is delayed or suppressed.
  - If the infant's serum is negative on screening, and there are no signs of congenital infection, no further testing is necessary.
- A positive IgM EIA test[52,53] and/or a sustained four-fold or greater difference of VDRL/RPR titre or TPPA titre above that of the mother (confirmed on testing a second specimen from the infant) indicates a diagnosis of congenital infection. Further investigations required:
  - Blood: full blood count, liver function, electrolytes
  - CSF: cells, protein, serological tests
  - X-rays of long bones
  - Ophthalmic assessment as indicated

Diagnosis in HIV-positive persons

- HIV-infected patients with early syphilis are more likely to have multiple, large and deep genital ulcers[54] and the risk of neurological complications may be higher in HIV-positive patients with early syphilis.[44,55,56] However, the clinical features in HIV-positive and negative individuals with early syphilis are often similar.[54,57]
- In a minority of cases, serology may be unreliable: there is a tendency for the RPR/VDRL titre to be lower in primary and statistically significantly higher in secondary syphilis,[57] although lower or false-negative titres have been

reported.[35,36,58] When clinical findings are suggestive of syphilis but serological tests are non-reactive, alternative tests (e.g. biopsy of a lesion, dark ground microscopy) may be useful for diagnosis.

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 clear and accurate written information.
- There is very little evidence to inform advice about the time sexual abstinence is required for 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 or until after the results of the first follow-up serology are known.
- 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,[59] 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.[60] Duration of treponemicidal levels of antimicrobial should be at least seven days to cover a number of division times (30–33 hours) of treponemes in early syphilis with a subtreponemicidal interval of not more than 24–30 hours.[59] 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.[61–66] 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.[67,68] Doxycycline has superceded the older tetracyclines; although 100 mg once or twice daily for 14 days is effective,[48,69] failure of once daily doxycyline has been reported.[70] One study of a single dose of 2 g of azithromycin has shown efficacy in early syphilis equivalent to that of benzathine penicillin[71] however there are concerns regarding azithromycin treatment failure[72] which appears to be linked to intrinsic macrolide resistance in some strains of *T. pallidum*.[73] In small studies, a number of ceftriaxone regimens have been shown to be effective.[74–81]
- The host immune response is important as 60% of untreated individuals go through life without developing late complications.[17] Although both benzathine penicillin G and standard regimens of procaine penicillin G do not achieve treponemicidal levels in CSF[82–87] 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 preparations.[88]
- Cardiovascular lesions may progress despite adequate treatment for syphilis. Steroid therapy is recommended in cardiovascular syphilis to prevent potential consequences of Jarisch–Herxheimer reaction. All patients with suspected cardiovascular syphilis should be reviewed by a cardiologist.
- Gummata affecting vital organs should be managed in collaboration with the appropriate specialist.
- For neurosyphilis 2.4 g (2.4 MU) i.m. o.d. for 10–14 days of procaine penicillin (plus probenecid 500 mg PO q.d.s. for the same duration) is the favoured dose in the Centers for Disease Control and Prevention (CDC) 2006 guidelines[48] as it has been shown to produce treponemicidal levels in the CSF,[89] although this may be an inconsistent finding.[92] It is likely that lower doses of procaine penicillin are as efficacious,[91] so a range of possible doses is given to reflect this and the available formulations of this drug. 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 been reported)[93].
- Both benzathine and procaine penicillins G are unlicensed in the UK. Practically, this means that:
  - The prescriber should be aware that the product is unlicensed and ensures 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 Trust 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 untoward patient reactions are recorded and reported to the Committee on the Safety of Medicines (CSM) via the yellow card scheme and to the Trust's critical incident report scheme.

Management in pregnancy: general considerations

- All pregnant women should be screened for syphilis at the initial antenatal visit.[93]
- Syphilis may be transmitted transplacentally at any stage of pregnancy[94–97] and may result in polyhydramnios, miscarriage, pre-term labour, stillbirth, hydrops and congenital syphilis.
- Maternal early stage syphilis[98–101] and high titre RPR/VDRL[102,103] are risk factors for congenital syphilis, although transmission rates of 10% in late latent disease have been reported.[104] Treatment in the last trimester is also associated

with poorer outcomes.[59,98,99,105–107] Maternal co-infection with HIV may increase the transmission risk of syphilis.[108–111]

- A single dose of Benzathine penicillin G 2.4 MU is effective in most cases,[102,112,113] although failures have been reported in case reports and small series; mainly in those at increased risk of transmission (higher RPR/VDRL titre, early stage maternal disease and last trimester treatment).[99,103] Physiological changes in pregnancy alter drug pharmacokinetics and may result in reduced penicillin concentrations.[114] For this reason, when maternal treatment is initiated in the third trimester a second dose of benzathine penicillin is recommended to be given one week after the first, with careful assessment of the neonate and consideration of treatment at birth.
- Re-treatment in those with a previous diagnosis of syphilis should be considered when there is uncertainty of efficacious past treatment, a four-fold drop in RPR/VDRL titre has not been achieved, or if the RPR/VDRL titre is serofast at greater than 1:8.
- Non-penicillin alternatives include ceftriaxone, for which there is limited data,[115] and erythromycin or azithromycin. There are no studies evaluating azithromycin in pregnancy and treatment failure has been reported with erythromycin[116,117] and azithromycin[118] with placental penetration uncertain;[119,120] for these reasons treatment of the baby at birth with penicillin is recommended following maternal treatment with macrolides.
- Desensitization to penicillin in those reporting allergies should be considered.[121,122]
- Management should be in close liaison with obstetric, midwifery and paediatric colleagues. Referral to fetal medicine for ultrasound to evaluate fetal involvement including non-immune hydrops or hepatospenomegaly and fetal monitoring for fetal distress in the early stages of therapy is recommended after 26 weeks gestation. Although there is a paucity of evidence in this area some physicians would use steroid therapy to avoid the Jarisch–Herxheimer reaction in order to avoid precipitating early labour. A large epidemiological study[123] reported an increase in the risk of orofacial cleft defects in children born to women who had received oral steroid treatment in the first trimester of pregnancy. Clinicians should discuss the balance of possible risk to perceived benefits with women before making a decision on use of adjunctive steroid treatment. Appropriate follow-up of babies is required (see congenital syphilis).

MANAGEMENT OF INFANTS BORN TO MOTHERS WITH SYPHILIS

- All infants to have serial serological tests for syphilis as detailed in the section 'Diagnosis of congenital syphilis' and have a thorough physical examination for signs of congenital syphilis; where these signs are suspected further investigations are indicated as detailed in the section above.
- For infants with suspected congenital syphilis and those born to mothers treated less than four weeks prior to delivery or those treated with non-penicillin regimens, or those who were not treated, who were inadequately treated or who have no documentation of being treated, treat for congenital syphilis 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 regimen more than four weeks prior to delivery with no evidence of re-infection or relapse, monitoring as detailed above is indicated. The CDC guidelines recommend a stat dose of Benzathine penicillin G 50,000 units/kg in this situation,[48] and treatment may be indicated particularly if follow-up is uncertain or if treatment was in the last trimester of pregnancy following the regimens detailed below.
- For infants born to mothers treated for syphilis prior to pregnancy with serofast titres, monitoring of the infants as detailed in the section 'Diagnosis of congenital syphilis' is indicated.
- Babies born to mothers treated antenatally for syphilis should be managed jointly with paediatricians.
- Older siblings should be screened for congenital syphilis.
- Congenital syphilis 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.

RECOMMENDED REGIMENS

Incubating syphilis/epidemiological treatment

(1) Benzathine penicillin G 2.4 MU i.m. single dose (III, B)
(2) Doxycycline 100 mg PO b.d. × 14 days (III, B)
(3) Azithromycin 1 g PO stat (III, B)

Early syphilis (primary, secondary and early latent)

(1) Benzathine penicillin G 2.4 MU i.m. single dose[55,71] (1b, A)
(2) Procaine penicillin G 600 000 units i.m. daily × 10 days[59,124–126] (III, B)

Early syphilis: alternative regimens

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

(1) Doxycycline 100 mg PO b.d. × 14 days (III, B)
(2) Azithromycin 2 g PO stat[71] (1b, B) or Azithromycin 500 mg daily × 10 days (II, B)
(3) Erythromycin 500 mg PO q.d.s. × 14 days[127] (III, B)
(4) Ceftriaxone 500 mg i.m. daily × 10 days (if no anaphylaxis to penicillin)
(5) Amoxycillin 500 mg PO q.d.s. plus Probenecid 500 mg q.d.s. × 14 days[128,129] (III, B)

Late latent, cardiovascular and gummatous syphilis

(1) Benzathine penicillin 2.4 MU i.m. weekly for two weeks (three doses) (III, B)
(2) Procaine penicillin 600,000 units i.m. o.d. for 17 days[130] (III, B)

Alternative regimens

(1) Doxycycline 100 mg PO b.d. for 28 days[131] (IV, C)
(2) Amoxycillin 2 g PO t.d.s. plus probenecid 500 mg q.d.s. for 28 days.[132] (III, C)

Neurosyphilis including neurological/ophthalmic involvement in early syphilis

(1) Procaine penicillin 1.8–2.4 MU i.m. o.d. plus probenecid 500 mg PO q.d.s. for 17 days[48,89] (III, C)

(2) Benzylpenicillin 18–24 MU daily, given as 3–4 MU i.m. every four hours for 17 days (III, C)

Alternative regimens

(1) Doxycycline 200 mg PO b.d. for 28 days[131] (IV, C)
(2) Amoxycillin 2 g PO t.d.s. plus probenecid 500 mg PO q.d.s. for 28 days[132] (IV, C)
(3) Ceftriaxone 2 g i.m. (with lidocaine as diluent) or i.v. (with water for injections as diluent, NOT Lidocaine) for 10–14 days[49,75–77,81,134–136] (IV, C) (if no anaphylaxis to penicillin)

Early syphilis in pregnancy

(1) Benzathine penicillin G 2.4 MU i.m. single dose in the first and second trimesters (II, B). When maternal treatment is initiated in the third trimester, a second dose of benzathine penicillin G 2.4 MU i.m. should be given after one week (day 8).
(2) Procaine penicillin G 600,000 unit i.m. daily × 10 days (III, B)

Alternative regimens

(1) Amoxycillin 500 mg PO q.d.s. plus probenecid 500 mg PO q.d.s. × 14 days (III, B)
(2) Ceftriaxone 500 mg i.m. daily × 10 days (III, B)
(3) Erythromycin 500 mg PO q.d.s. × 14 days or Azithromycin 500 mg PO daily × 10 days *plus* evaluation and treatment of neonates at birth with penicillin (III, B)

Late syphilis in pregnancy

Manage as in non-pregnant patients but without the use of doxycycline.

Syphilis in HIV-positive individuals

Treatment as appropriate for the stage of infection; that is, HIV-positive individuals to be given the same treatment regimens as HIV-negative individuals. Some experts believe that HIV patients with syphilis should be treated as for neurosyphilis to prevent the development of neurological involvement, but hard evidence for this policy is lacking.

Congenital syphilis

(1) Benzyl penicillin sodium 100,000–150,000 units/kg daily i.v. (in divided doses given as 50,000 units/kg 12 hourly in the first 7 days of life and 8 hourly thereafter) × 10 days (III, B)
(2) Procaine penicillin 50,000 units/kg daily i.m. × 10 days (III, B)

In children, intravenous therapy (option one here) may be preferable due to the pain associated with intramuscular injections (Table 2).

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 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 and resolving within 24 hours. This is common in early syphilis but is usually not important unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour. It is uncommon in late syphilis but can potentially be life threatening if there is involvement of strategic sites (e.g. coronary ostia, larynx and nervous system). Prednisolone can reduce the febrile episode[136] but is not proven to ameliorate local inflammation. Nevertheless, severe clinical deterioration in early syphilis with optic neuritis and uveitis has been reported following treatment and, as a steroid is also used in the management of these conditions unrelated to syphilis, biological plausibility would suggest that it may help. If cardiovascular or neurological involvement including optic neuritis, inpatient management is advisable. Management should include antipyretics and reassurance. Steroids are recommended when there is neurological or cardiovascular involvement and some physicians recommend this treatment in pregnancy when additional fetal monitoring is required.
  - Prednisolone 40–60 mg daily for three days, starting antitreponemal treatment 24 hours after commencing prednisolone (IV, C).
- Procaine reaction, (procaine psychosis, procaine mania, Hoignes syndrome): This is due to inadvertent intravenous injection of procaine penicillin. It is characterized by fear of impending death and may cause hallucinations or fits immediately after injection and lasting less than 20 minutes. Calm and verbal reassurance is required and restraint may be necessary. If fits occur give diazepam 10 mg rectally.
- Anaphylactic shock: Facilities for treatment of anaphylaxis should be available as penicillin is amongst the commonest cause.
  - Epinephrine (adrenaline) 0.5 mg i.m. (as 0.5 mL of 1:1000 solution) followed, if necessary, by i.m./i.v. antihistamine e.g. chlorpheniramine 10 mg and i.m./i.v. hydrocortisone 100 mgM
- Allergy: Penicillin desensitization may be considered for patients reporting penicillin allergy.[121,122] Many people reporting penicillin allergy will not display hypersensitivity on re-exposure to penicillin either because the hypersensitivity has faded or they were never allergic to penicillin. A careful history may help to identify the latter group. Skin testing to confirm allergy should precede desensitization. Skin testing and desensitization do carry risks of anaphylaxis and should be carried out with immediate access to resuscitation equipment and expertise.

Management of sexual partners

- All patients with a diagnosis of syphilis should have partner notification discussed at the time of treatment by a trained health-care professional.
- For patients with primary syphilis, sexual partners within the past three months should be notified as the incubation

period is up to 90 days. Partner notification may have to extend to two years for patients in secondary syphilis, with clinical relapse or in early latent syphilis. Of contactable sexual partners of patients and pregnant women with early syphilis 46–60% also have the infection.[137,138] Many sexual contacts are met in anonymous sex venues e.g. saunas, internet or cruising grounds,[139–141] which makes partner notification difficult. Links within high-risk venues to provide screening and advice may prove useful.[140]

- Epidemiological treatment for asymptomatic contacts of early syphilis should be considered unless partners are able to attend regularly for exclusion of syphilis.
- 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 partner notification activities. Individuals with late latent syphilis are usually unable to transmit the infection to sexual partners. Although vertical transmission may occur at any time within 10 years of initial infection, this becomes unusual more than two years after the onset of early syphilis. It is reasonable for sexual partners and children born to women diagnosed with late latent syphilis of unknown duration to undergo screening to diagnose or exclude infection.
- All patients should be offered patient and provider referral as a method of contacting any sexual partners. The method agreed upon with the patient should be clearly documented.

Follow-up

The follow-up is in case of re-infection and relapse.

- For early syphilis, minimum clinical and serological (VDRL or RPR) follow-up should be at months 1, 2, 3, 6 and 12, then six monthly until VDRL/RPR negative or serofast.
- For late syphilis minimum serological follow-up is three monthly until serofast.
- A sustained two bottle dilution (i.e. four-fold) or greater increase in the VDRL or RPR titre suggests re-infection or treatment failure. Treatment failure is characterized by
  - Four-fold or greater increase in non-treponemal test titre
  - Recurrence of signs or symptoms
  - Re-infection excluded
- CSF examination and re-treatment is indicated and should also be considered for persons whose non-treponemal test titres do not decrease four-fold within 6–12 months of therapy. The majority of specialists would re-treat patients

Table 2 **Recommended treatment regimens**

Clinical stage	Recommended regimens	Alternative regimen	Clinical notes
Incubating syphilis/ epidemiological treatment	(1) Benzathine penicillin 2.4 MU i.m. single dose (2) Doxycycline 100 mg PO b.d. × 14 days (3) Azithromycin 1 g PO stat		
Early (primary/ secondary/ early latent) syphilis	(1) Benzathine penicillin 2.4 MU i.m. single dose 2.Procaine penicillin G 600 000 units i.m. daily × 10 days	(1) Doxycycline 100 mg PO b.d. × 14 days (2) Azithromycin 2 g PO stat or Azithromycin 500 mg daily × 10 days (3) Erythromycin 500 mg PO q.d.s. × 14 days (4) Ceftriaxone 500 mg i.m. daily × 10 days (5) Amoxycillin 500 mg PO q.d.s. plus Probenecid 500 mg	
Late latent, cardiovascualr and gummatous syphilis	(1) Benzathine penicillin 2.4 MU i.m. weekly for two weeks (three doses) (2) Procaine penicillin 600,000 units i.m. OD for 17 days	(1) Doxycycline 100 mg PO b.d. for 28 days (2) Amoxycillin 2 g PO t.d.s. plus probenecid 500 mg q.d.s. for 28 days	Steroid cover should be given when treating cardiovascular syphilis
Neurosyphilis	(1) Procaine penicillin 1.8–2.4 MU i.m. OD plus probenecid 500 mg PO q.d.s. for 17 days (2) Benzylpenicillin 18–24 MU daily, given as 3–4 MU i.v. every 4 hours for 17 days	(1) Doxycycline 200 mg PO b.d. for 28 days (2) Amoxycillin 2 g PO t.d.s. plus probenecid 500 mg PO q.d.s. for 28 days (3) Ceftriaxone 2 g i.m. OD for 10–14 days	
Treatment of early syphilis in pregnancy	(1) Benzathine penicillin 2.4 MU i.m. 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 i.m. should be given after one week (day 8). (2) Procaine penicillin G 600,000 unit i.m. daily × 10 days	(1) Amoxycillin 500 mg PO q.d.s. plus probenecid 500 mg PO q.d.s. × 14 days (2) Ceftriaxone 500 mg i.m. daily × 10 days (3) Erythromycin 500 mg PO q.d.s. × 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. Appropriate follow-up of babies is required.
Treatment of late syphilis in pregnancy	Manage as in non-pregnant patient but without the use of doxycycline		
Syphilis treatment in HIV-positive people	Treatment as appropriate for the stage of infection		
Congenital syphilis	(1) Benzyl penicillin sodium 100,000–150,000 units/kg daily i.v. (in divided doses given as 50,000 units/kg 12 hourly in the first 7 days of life and 8 hourly thereafter) × 10 days (2) Procaine penicillin 50,000 units/kg daily i.m. × 10 days		In children intravenous therapy (option one here) may be preferable due to the pain associated with intramuscular injections.

with benzathine penicillin G administered as three doses of 2.4 million units i.m. each at weekly intervals, if CSF examinations are normal.
- Specific treponemal tests may remain positive for life following effective treatment; clear documentation is necessary to prevent unnecessary re-treatment.
- Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance, and sexual partners should be screened and treated.
- If the patient remains asymptomatic and the VDRL/RPR is negative or serofast at one year, the patient may be discharged.
- In those with concomitant HIV infection, initial follow-up as above and then lifelong monitoring with syphilis serology at least annually and in outbreak situations three monthly (coinciding with HIV follow-up visits).

Auditable outcome measures

- Performing VDRL/RPR titre at commencement of therapy
- Response to treatment:
  - Resolution of clinical lesions
  - A two dilution (four-fold) or greater titre decrease in the VDRL/RPR within three to six months after treatment
  - For neurosyphilis, the CSF cell count should have decreased by six months and the CSF should be entirely normal by two years except for persistent positive specific tests.
  - Ninety-five percent of patients with early syphilis should complete treatment.
- At least 60% of contactable partners should attend for screening and/or treatment (although while this standard may be achievable in some settings it may not be in all).

EVIDENCE BASE

Members of the guidelines revision group conducted literature reviews that included searching Medline for the years 1970–2007 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 1996–present was also conducted. Only English language papers were used.

Previous guidelines were sought, and the 2006 CDC guidelines reviewed. The previous 2001 guidelines were used as a basis.

EDITORIAL INDEPENDENCE

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APPENDIX 1

- Acquiring Procaine Penicillin G and Benzathine Penicillin G: Refer to the BASHH website for guidance (2006) on obtaining supplies of Procaine Penicillin G and Benzathine Penicillin G: http://www.bashh.org/guidelines/penicillin_update_0306.pdF

- Administering Benzathine penicillin intramuscularly can be very painful for patients, this may be substantially improved by using lidocaine as the diluent: (Protocol from Manchester Centre for Sexual Health courtesy of Matron Helen Hodgson)

This protocol is to be used for the reconstitution of Benzathine penicillin for the treatment of syphilis.

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

Presentation: Powder for solution for injection

Contraindications:

Allergy to penicillin or lignocaine

Concomitant anticoagulant therapy

Bleeding diathesis (e.g. Haemophilia)

Precautions: Cross allergy to other beta-lactams such as cephalosporins should be taken into account.

Administration: To reduce the pain experienced by patients receiving this injection, 1% lidocaine (lignocaine) can be used as an alternative diluent to water for injections (unlicensed indication).

Reconstitute the vial with 8 mL of 1% Lidocaine Hydrochloride BP solution. Split the resultant solution into two equal volumes.

The solution should be administered by deep intramuscular injection on two different sites.

Solutions in Lidocaine MUST NOT be administered intravenously.

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

Reference

Lidocaine as a diluent for administration of benzathine penicillin G. *Pediatr Infect Dis J* 1998;**17**:890–3

APPENDIX 2

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