

UK National Guidelines on the Management of Early Syphilis

Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases).

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, tertiary including gummatous, cardiovascular and neurological involvement, the latter two are also sometimes classified as quaternary) syphilis. Congenital syphilis is divided into early (first 2 years) and late including stigmata of congenital syphilis.

Clinical Features¹⁻³

- Primary syphilis is characterised by an ulcer (the chancre) and regional lymphadenopathy. The chancre is classically in the anogenital region, single, painless and indurated with a clean base discharging clear serum. However chancres may be atypical: multiple, painful, purulent, destructive, may cause the syphilitic balanitis of Follman⁴, and may be extragenital. There may also be a mixed aetiology⁵. Any anogenital ulcer should be considered to be syphilitic or herpetic unless proven otherwise. Herpetic ulcers may be atypical, and the chronic mucocutaneous anogenital herpes occurring with HIV can mimic a chancre. Chancroid, lymphogranuloma venereum and donovanosis should be considered if the ulcer is acquired in the tropics.
- Secondary syphilis is characterised by multisystem involvement within the first two years of infection: generalised polymorphic rash often affecting the palms and soles, condylomata lata, mucocutaneous lesions, generalised lymphadenopathy; less commonly, patchy alopecia, anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periosteitis and glomerulonephritis.⁶⁻¹¹ The rash is classically non-itchy but may be itchy, particularly in dark-skinned patients.¹²
- Early latent syphilis is characterised by positive serological tests for syphilis with no clinical evidence of treponemal infection within the first two years of infection.

History

- Syphilitic lesions
- Past treatment, eg a course of penicillin injections

- Obstetric history, eg miscarriages, stillbirths in women
- If positive serological tests for treponemal infection in the absence of clinical signs, i) exclude other treponemal infection such as yaws, bejel and pinta depending on country of origin, eg consider yaws if from the Caribbean; pinta for Central America. Yaws is a disease of childhood in the countryside of endemic areas and may typically affect the legs, which heal with tissue paper scars. A VDRL/RPR titre of > 1:8 in an adult suggests syphilis, as adults with late yaws usually have low titres. ii) If latent syphilis is of unknown duration, then early latent infection may be suggested by sexual history of contact with a possible source, past history of early syphilitic lesions within two years, absence of late syphilitic complications, and high VDRL/RPR titres. iii) If latent syphilis is diagnosed, decide whether is acquired or congenital. Pointers to congenital syphilis include history suggestive of acquired syphilis in parents, congenital syphilis in siblings and presence of stigmata of congenital syphilis in patients.

Diagnosis

Demonstration of *Treponema pallidum*

(From lesions or infected lymph nodes in early syphilis)

- Dark field microscopy
- Direct fluorescent antibody (DFA) test
- PCR⁵ – provided as a reference test by Genitourinary Infections Reference Laboratory, PHLS, Bristol (DFA and PCR can be used for oral or other lesions where contamination with commensal treponemes is likely)

Serological Tests for Syphilis

- Cardioliipin (reaginic) tests: Venereal Diseases Research Laboratory (VDRL) carbon antigen test/rapid plasma reagin test (RPR)
- Specific tests: treponemal enzyme immunoassay (EIA) to detect IgG, IgG & IgM, or IgM, *Treponema pallidum* haemagglutination assay (TPHA), *Treponema pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorption test (FTA-abs)
- Treponemal EIA (preferably IgG & IgM) or VDRL/RPR and TPHA/TPPA are recommended for screening¹³
- Request EIA for anti-treponemal IgM¹⁴⁻¹⁷ if primary syphilis is suspected – IgM is detectable towards the end of second week of infection while IgG is detectable usually in the fourth or fifth week.¹⁸
- A false negative cardioliipin (reaginic) test may occur in secondary or early latent syphilis due to the prozone phenomenon from using undiluted serum
- 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^{19,20,21}
- Always repeat positive tests to confirm the result

- Repeat serological tests in cases of anogenital ulceration at 3 months if initial tests were negative.
- Serological tests cannot differentiate from other treponemal infections – for example, yaws

Confirmation or exclusion of neurological, cardiovascular or ophthalmic involvement:

- Lumbar puncture not necessary in secondary/early latent syphilis unless clinical evidence of neurological involvement
- CXR in latent syphilis
- Ophthalmic assessment (slit lamp) may be helpful to differentiate between acquired or congenital syphilis (interstitial keratitis) in cases of latent infection of uncertain duration where congenital syphilis is suspected.

Management: General Considerations

- A treponemicidal level of antimicrobial should be achieved in the serum, and in the CSF in the case of neurosyphilis. A penicillin level of >0.018 mg/l is considered treponemicidal²², 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.²³
- Duration of treponemicidal levels of antimicrobial should be at least 7 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.²² 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.²⁴⁻²⁹ To provide a "safety margin" daily parenteral treatment is given for 10 days in early syphilis and 17 days in late syphilis and in early syphilis with neurological involvement. Clinical data is lacking on the optimal dose, 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 past clinical experience. To standardise therapy the above treatment durations are used for this guideline.
- 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 are tetracyclines including doxycycline, and erythromycin. Erythromycin is least effective and does not penetrate the CSF or placental barrier well.^{30,31} Doxycycline has superseded the older tetracyclines; although 100 mg once or twice daily for 14 days is effective³²⁻³³, failure of the latter regimen for early latent syphilis has been reported³⁴. Newer antitreponemal regimens include azithromycin and ceftriaxone; the latter has good CSF penetration. They may be considered as treatment options although more data are desirable. Azithromycin 0.5 or 1 g stat, followed by 500 mg daily for a total of 10 days was effective for early syphilis³⁵⁻³⁷. In small studies ceftriaxone has been shown to be effective³⁸⁻⁴⁴ with dosages starting from 250 mg daily for 10 days but many physicians

in the American Emerging Infections Network used 1- 2 g im or iv for varying duration⁴⁵.

- The host immune response is important as 60% of untreated patients go through life without developing late complications.⁴⁶ CSF involvement is common in early syphilis. Although both benzathine penicillin and standard regimens of procaine penicillin G do not achieve treponemicidal levels,⁴⁷⁻⁵² 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. However, the use of benzathine penicillin rather than procaine penicillin G, has been associated with failure in pregnant women^{27,53,54,55} and in an immunocompetent patient⁵⁶ as well as those with concomitant HIV infection.⁵⁷⁻⁶³ A single dose of 2.4 MU benzathine penicillin in asymptomatic neurosyphilis showed a 21 % CSF relapse rate which was twice that of other penicillin preparations.⁶⁴
- Procaine penicillin G is available as 'Jenacillin O' which contains procaine penicillin G in aluminium stearate and peanut oil and as 'Jenacillin A' which contains both procaine penicillin G and penicillin G sodium. Recommended dosage of procaine penicillin G is 600mg /600,000 u. daily in early syphilis and 1.8 to 2.4 g/1.8-2.4 MU daily in late syphilis but would lead to fraction of a ml using Jenacillin A. To make it easier for administration, it is recommended that a slightly higher dosage of procaine penicillin G be given. (See Appendix 1.)
- Compliance with daily intramuscular injections with procaine penicillin G has been shown to be good.⁶⁵ This regimen has been the treatment of choice in the UK. The control of syphilis over the past 50 years in the UK has been excellent and the fact that late complications of syphilis are uncommon with hardly any report of failures, even in patients with concomitant HIV infection indicate that this regimen has been effective.
- All patients should be offered screening for other sexually transmitted infections including HIV.
- When there is an outbreak of early syphilis, it is advisable to screen sexually active patients attending Genitourinary Medicine or HIV clinics for syphilis every three months.

Specific Treatment

Incubating Syphilis/Epidemiological Treatment

- First line therapies:
 - i.m Benzathine penicillin 2.4 MU x 1 (Evidence level : III B)
 - Doxycycline 100mg BD x 14 days (Evidence level : III B)
- Second line therapy:
 - Azithromycin 1 g stat (Evidence level : III B)

Early Syphilis (Primary, Secondary And Early Latent)

- First line therapies:
 - im Procaine penicillin G 750mg daily (Jenacillin A 3 ml or Jenacillin O 2.5 ml) x 10 days^{22,66,67} . (Evidence level : III B)
If unable to give daily procaine penicillin on the weekend, give either 1. long acting Procaine penicillin G in aluminium stearate (Jenacillin O) 2 MU or long acting Biclinocillin i.m. 2 MU (containing benethamine penicillin 1.2 MU) on Friday to cover the weekend
 - im Benzathine penicillin 2.4 MU single dose, or x 2 (day 1 and 8)^{68,69} (Evidence level : III B)
- Penicillin Allergy
 - Doxycycline 100mg BD x 14 days (Evidence level : III B)
 - Erythromycin 500mg QDS x 14 days⁷¹ (Evidence level : III B)
 - Other options: Azithromycin 500 mg daily x 10 days³⁵⁻⁴⁰
i.m. Ceftriaxone 500mg daily x 10 days (if no anaphylaxis to penicillin)
- Parenteral treatment refused
 - Amoxicillin 500mg QDS plus Probenecid 500mg QDS x 14 days^{71,72} (Evidence level : III B)
 - As for penicillin allergy

Neurological/Ophthalmic Involvement in Early Syphilis or If Neurosyphilis Cannot Be Excluded

Biological plausibility suggests that regimens that achieve treponemicidal levels of antimicrobial in the CSF should be the treatment of choice. There is little data on how this translates into long term clinical efficacy. Treat as for neurosyphilis (see section on Management of Late Syphilis)

Pregnancy:

All pregnant women should be screened for syphilis at the initial antenatal visit.⁷³ In pregnant women with untreated early syphilis, 70-100% of infants will be infected with stillbirths in up to one-third of cases. Patients should be jointly managed with obstetricians and midwives. All pregnant women with positive treponemal serology should be evaluated for clinical evidence of syphilis and treated as for syphilis. To minimize default, treatment may need to be initiated before a confirmatory second serology is available.

Women who had documented treatment for syphilis in the past do not need retreatment during current or subsequent pregnancies if there is no clinical evidence of syphilis and the VDRL or RPR titre is negative or serofast in low titre compared to previous results. However it is important that reinfection is excluded by checking the partner and babies should be followed-up by a paediatrician to exclude congenital syphilis.

- First line:
 - im Procaine penicillin G 750mg (Jenacillin A 3 ml or Jenacillin O 2.5 ml) daily x 10 days. (Evidence level : III B)
If unable to give daily procaine penicillin on the weekend, to give either long acting Procaine penicillin G in aluminium stearate (Jenacillin O) 2 MU or long acting Biclinocillin i.m. 2 MU (containing benethamine penicillin 1.2 MU) on Friday to cover the weekend.
- Penicillin allergy
 - Erythromycin 500mg QDS x 14 days plus examination, tests and treatment of all babies at birth (see congenital syphilis).⁷⁴⁻⁷⁶
(Evidence level : III B)
 - Other option: Azithromycin 500mg daily x 10 days plus examination, tests and treatment of all babies at birth
 - Desensitisation to penicillin may be considered followed by first line treatment (see management of late syphilis for desensitisation schedule).⁷⁷
 - Mothers treated with erythromycin or azithromycin may be considered for retreatment with doxycycline after delivery and when breast-feeding is stopped.
- Non-Compliance Suspected
 - Benzathine penicillin 2.4 MU IM weekly x 2 (day 1 and 8)
(Evidence level : III B)

Congenital Syphilis

Babies born to mothers treated antenatally for syphilis should be managed jointly with paediatricians.

- Diagnosis
 - Clinical evidence of congenital syphilis:^{1,78,79}
 - Early (first two years)– rash including condylomata lata, vesiculo-bullous lesions, snuffles, haemorrhagic rhinitis, osteochondritis, periostitis, pseudoparalysis, mucous patches, perioral fissures, hepatosplenomegaly, generalised lymphadenopathy, non-immune hydrops, glomerulonephritis, neurological or ocular involvement, haemolysis, 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.

- Laboratory evidence of congenital syphilis:
 - Serological tests should be performed on infant's blood not cord blood
 - Serological tests that detect IgG may be positive due to passive transfer of maternal antibodies whether or not the infant is infected (positive tests due to passively transferred antibody should be negative by 6 months)
 - A positive anti-treponemal EIA IgM^{80,81} is consistent with a diagnosis of congenital infection
 - Always repeat positive tests to confirm results.
 - A negative IgM test should be repeated at 4, 8 and 12 weeks as the IgM response might be delayed or suppressed
 - Quantitative VDRL/RPR may be useful for diagnosis if the titre is more than two dilutions (fourfold increase) above the mother's titre
 - Serological tests can be negative in infants infected in late pregnancy and should be repeated.
 - Darkfield microscopy from early congenital syphilitic lesions or body fluids
 - Blood: Full blood count, liver function, electrolytes
 - CSF : cells, protein, VDRL in late congenital syphilis
 - X-rays long bones
 - Ophthalmic assessment as indicated
- Treatment
 - i.v. benzyl penicillin sodium 100,000 - 150,000 u/kg daily (in divided doses given as 50,000u/kg 12 hourly in the first 7 days of life and 8 hourly thereafter) x 10 days. (Evidence level : III B)
 - i.m. procaine penicillin G 50,000 u/kg daily x 10 days (Jenacillin A 0.2 ml/Kg) (Evidence level : III B)
- Follow-up
 - Minimum clinical and serological (VDRL or RPR) follow-up should be at 3 months, 6 months and 1 year.
- Other issues
 - 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 should be screened for syphilis.

HIV Infected Patients

Serological tests for syphilis in patients with both syphilis and HIV are generally reliable although false negative tests and delayed appearance of seroreactivity have been reported^{20,19}. HIV infected patients with early syphilis may have an increased risk of neurological involvement, unusual neurological manifestations, and higher rate of treatment failure with benzathine penicillin including more frequent serological relapse and lower rate of elimination of treponemes.^{57-63, 69, 82-86}.

There may also be rapid progression to gummatous syphilis.^{87,88} HIV infected patients also commonly have neurological abnormalities which may be difficult to differentiate from neurosyphilis. It could be argued that treatment for neurosyphilis should be given to all HIV positive individuals with syphilis so that neurosyphilis is a less likely part of the differential diagnosis if neurological symptoms or signs are currently present or develop subsequently.

- Treatment

- As for neurosyphilis (see Management of Late Syphilis)

- Reactions To Treatment

Patients should be warned of possible reactions to treatment. Facilities for resuscitation should be available in the treatment area.

- Jarisch-Herxheimer Reaction

An acute febrile illness with headache, myalgia, chills and rigors 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 (eg coronary ostia, larynx, nervous system). Prednisolone can reduce the febrile episode⁸⁹ 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. As a steroid is also used in the management of these conditions unrelated to syphilis, biological plausibility would suggest that it may help.

- Management

- If cardiovascular or neurological involvement including optic neuritis, inpatient management is advisable:

Prednisolone 10-20mg three times daily for 3 days, starting anti treponemal treatment 24 hours after commencing prednisolone.

(Evidence level : IV C)

- Antipyretics

- Procaine reaction, (procaine psychosis, procaine mania, Hoignes syndrome)

This is due to inadvertent intravenous injection of procaine penicillin and may be minimised by the "aspiration technique" of injection. It is characterised by fear of impending death and may cause hallucinations or fits immediately after injection and lasting less than 20 minutes.

- Management

- Exclude anaphylaxis
- Calm and verbal reassurance; restraint may be necessary.
- If fits, Diazepam 10 mg rectally or 10 mg IV at a rate of not more than 5mg per minute or 10 mg IM.

- Anaphylactic shock

Facilities for treatment of anaphylaxis should be available as penicillin is amongst the commonest cause.

- Management
 - Epinephrine (Adrenaline) 1:1000 IM 0.5ml followed by
 - IM/IV antihistamine eg chlorpheniramine 10mg
 - IM/IV hydrocortisone 100mg.

Management of contacts

- All patients with syphilis should be seen for partner notification, health education and confirmation of any past treatment history.
- 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 2 years for patients in secondary syphilis with clinical relapse or in early latent syphilis.
- 46-60 % of contactable sexual partners of patients and pregnant women with early syphilis also have the infection.^{90,91}
- Epidemiological treatment for asymptomatic contacts of early syphilis should be considered unless partners are able to attend regularly for exclusion of syphilis. Serological tests for syphilis including EIA IgM or FTA-abs should be performed at the first visit and repeated at 6 weeks and 3 months.

Follow-Up

The follow-up is for both reinfection and relapse.

- For early syphilis, minimum clinical and serological (VDRL or RPR) follow-up should be monthly for 3 months, 6 months and 1 year.
- Early clinical relapse tends to occur in the oral and anal regions.
- A sustained two dilution (fourfold) or greater increase in the VDRL or RPR titre suggests re-infection or treatment failure
- Specific treponemal tests may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary retreatment. Patients should also be given a letter documenting their treatment.
- Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance, and sexual partners should be rescreened.
- If the patient remains asymptomatic and the VDRL/RPR is negative or serofast at one year, the patient may be discharged.
- Those with concomitant HIV infection or on non-penicillin treatment should be followed up annually for life.

Auditable outcome measures

Response to treatment:

- Resolution of clinical lesions
- A two dilution (fourfold) or greater titre decrease in the cardiolipin (reaginic) tests within 3-6 months after treatment
- For neurosyphilis, the CSF cell count should have decreased by 6 months and the CSF should be entirely normal by 2 years except for persistent

positive specific tests.

- 95% of patients with early syphilis should complete treatment.
- At least 60% of contactable partners should attend for screening and/or treatment.

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Conflict of interest:

None

Evidence base

Medline was searched for the years 1965 to 2000 using keywords: "syphilis", "human", "English", "diagnosis", "therapy".

Other key review papers: references 22, 32, 92, 93

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Appendix 1.

1. Benzathine penicillin (Extencilline, Penidural), Biclinocillin, Jenacillin A, Jenacillin O and probenecid are available on a named patient basis in the UK and can be obtained through Idis World Medicine, Millbank House, 171-185 Ewell Road, Surbiton, Surrey KT6 6AX. Tel: 020-84100710, Fax: 020-84100800, E-mail: hospitals@idis.co.uk

2. Jenacillin A and O

Procaine penicillin G is available in the form of Jenacillin A and O.

Each vial of Jenacillin A 2 megaunits (2MU) contains 1.5MU (1.5g) of procaine penicillin G and 0.5MU (300g) penicillin G sodium. For the purposes of dose calculation for the treatment of syphilis, the penicillin G sodium component is ignored.

Each vial of Jenacillin O contains 2 g/2 MU of procaine penicillin G in 6.7 ml of oily suspension (aluminium monostearate and peanut oil). Jenacillin O is contraindicated in patient allergic to peanuts.

Reconstitution of Jenacillin A

Each vial of Jenacillin A is reconstituted with 4.5ml Water for injection to make a final volume of 6 ml containing 1.5 g of procaine penicillin g. Each vial should be used immediately after reconstitution.

The table below illustrates the doses and volumes of Jenacillin A or O to be administered:

Stage of Syphilis	Procaine Penicillin G dose		Volume of to administer (ml)	
	Units	mg	Jenacillin A	Jenacillin O
Early Congenital	50,000 U/kg	50/kg	0.2ml/kg	0.18ml/kg
Early/Late	750,000 U	750	3	2.5
Neurosyphilis	2 MU	2000	8 (4ml/ buttock)	6.7 (1 vial) (half in each buttock)

3. One vial of Biclinocillin containing 0.6 MU of Benethamine penicillin G and 0.4 MU of penicillin G sodium is reconstituted to give 3 ml of solution per vial. As in the case of Jenacillin A, the penicillin G sodium component is ignored in the dosage

calculation. Six mls (3 ml in each buttock) containing 1.2 MU of benethamine is given.

4.Administration

Benzathine penicillin, Biclinocillin and Jenacillin A are given by deep intramuscular injection into the dorsogluteal muscle or the vastus lateralis muscle.⁹⁴