3.4. SYPHILIS

CLINICAL PRESENTATION SUMMARY

Syphilis is a systemic disease from the outset and is caused by the spirochaete, *Treponema pallidum* (*T. pallidum*). The infection can be classified as congenital (transmitted from mother to child *in utero*) or acquired (through sex or blood transfusion).

Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, gummatous, neurological and cardiovascular syphilis.

Primary syphilis is characterised by an ulcer or chancre at the site of infection or inoculation. Secondary syphilis manifestations include a skin rash, condylomata lata, mucocutaneous lesions and generalised lymphadenopathy.

As its name implies, latent syphilis has no clinical manifestations. Early latent syphilis is infection of less than two years duration. An infection of more than two years duration without clinical evidence of treponemal infection is referred to as late latent syphilis. WHO has based this division on the infectiousness of syphilis and its response to therapy. Early stages are more infectious but respond better to treatment.

In the early phase of primary syphilis the cardiolipin/non-treponemal tests, such as the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests may be negative and should, therefore, not be interpreted as absence of syphilis infection.

**Therapeutic considerations**

A treponemicidal level of antimicrobials needs to be achieved in the serum and cerebrospinal fluid (CSF) to provide effective treatment for syphilis. A penicillin level of greater than 0.018 mg per litre is considered sufficient, and needs to be maintained for at least 7–10 days in early syphilis, and for a longer duration in late syphilis. Long-acting benzathine benzylpenicillin, at a dose of 2.4 million
units, provides a treponemicidal penicillinaemia for up to three weeks and is recommended for late syphilis treatment.

Parenteral, rather than oral, penicillin treatment is preferred as it provides guaranteed bioavailability and supervised treatment. More data are required before either ceftriaxone or oral azithromycin can be generally recommended. Azithromycin has the advantage of being effective against *C. trachomatis, H. ducreyi* and the gonococcus.

Management of patients with cardiovascular syphilis should include consultation with a cardiologist. All patients with cardiovascular syphilis and neurosyphilis should be monitored for many years. The follow-up should include clinical, serological, CSF and, based on the clinician’s assessment of the individual patient’s condition, radiological examinations.

**Follow-up of patients treated for syphilis**

The follow-up of patients treated for early syphilis should be based on available medical services and resources. The clinical condition of the patients should be assessed and attempts made to detect reinfection during the first year after therapy. Patients with early syphilis who have been treated with appropriate doses and preparations of benzathine benzylpenicillin should be evaluated clinically and serologically, using a non-treponemal test, after three months to assess the results of therapy. A second evaluation should be performed after six months and, if indicated by the results at this point, again after 12 months to reassess the condition of the patient and detect possible reinfection.

At all stages of the disease, repeat treatment should be considered when:

- clinical signs or symptoms of active syphilis persist or recur;
- there is confirmed increase in the titre of a non-treponemal test.

Examination of the CSF should be undertaken before repeat treatment, unless reinfection and a diagnosis of early syphilis can be established. Patients should be re-treated with the schedules recommended for syphilis of more than two years’ duration. In general, only one re-treatment course is indicated because adequately treated patients often maintain stable, low titres of non-treponemal tests.
SYPHILIS AND HIV INFECTION

All patients with syphilis should be encouraged to undergo testing for HIV infection because of the high frequency of dual infection and its implications for clinical assessment and management. Neurosyphilis should be considered in the differential diagnosis of neurological disease in HIV-infected individuals. In cases of congenital syphilis, the mother should be encouraged to undergo testing for HIV; if her test is positive, the infant should be referred for follow-up.

Recommended therapy for early syphilis in HIV-infected patients is no different from that in patients not infected with HIV. However, some authorities advise examination of the CSF and/or more intensive treatment with a regimen appropriate for all patients with the dual infections of *T. pallidum* and HIV, regardless of the clinical stage of syphilis. In all cases, careful follow-up is necessary to ensure adequacy of treatment.

SYPHILIS IN PREGNANCY

Pregnant women should be regarded as a separate group, requiring close surveillance, in particular to detect possible reinfection after treatment has been given. It is also important to treat their sexual partner(s). Pregnant patients at all stages of pregnancy, who are not allergic to penicillin, should be treated with penicillin according to the dosage schedules recommended for the treatment of non-pregnant patients at a similar stage of the disease.

The effectiveness of erythromycin in all stages of syphilis and its ability to prevent the stigmata of congenital syphilis are both highly questionable, and many failures have been reported. Its efficacy in neurosyphilis is probably low. Although data are lacking, consideration should probably be given to using an extended course of a third-generation cephalosporin in pregnant women whose penicillin allergy is not manifested by anaphylaxis.

Penicillin desensitisation of pregnant women with syphilis requires that the procedure be performed in a hospital setting. This is not feasible at most primary health care settings and cannot be recommended as a routine procedure.
Follow-up

Following treatment, quantitated non-treponemal serological tests should be performed at monthly intervals until delivery, and re-treatment should be undertaken if there is serological evidence of reinfection or relapse.

CONGENITAL SYPHILIS

Congenital syphilis is divided into early (first two years of life) and late (becomes apparent later in life).

Prevention of congenital syphilis is feasible. Programmes should implement effective screening strategies for syphilis in pregnant women. Screening for syphilis should be conducted at the first prenatal visit. Some programmes have found it beneficial to repeat the tests at 28 weeks of pregnancy and at delivery in populations with a high incidence of congenital syphilis.

Congenital syphilis may occur if the expectant mother has syphilis, but the risk is minimal if she has been given penicillin during pregnancy. All infants of seropositive mothers should be examined at birth and at monthly intervals for three months until it is confirmed that serological tests are, and remain, negative. Any antibody carried over from mother to baby usually disappears within three months of birth. Where available, IgM-specific serology may aid diagnosis.

All infants born to seropositive mothers should be treated with a single intramuscular dose of benzathine benzylpenicillin, 50 000 IU/kg whether or not the mothers were treated during pregnancy (with or without penicillin). Hospitalization is recommended for all symptomatic babies born to mothers who were seropositive. Symptomatic infants and asymptomatic infants with abnormal CSF (up to two years of age) should be treated as for early congenital syphilis.

Early congenital syphilis generally responds well, both clinically and serologically, to adequate doses of penicillin. Recovery may be slow in seriously ill children with extensive skin, mucous membrane, bone or visceral involvement. Those in poor nutritional condition may succumb to concurrent infections, such as pneumonia.
TREATMENT REGIMEN FOR SYphilis

EARLY SYphilis

(primary, secondary, or latent syphilis of not more than two years’ duration)

Recommended regimen

- benzathine benzylpenicillin,\(^8\) 2.4 million IU by intramuscular injection, at a single session. Because of the volume involved, this dose is usually given as two injections at separate sites

Alternative regimen

- procaine benzylpenicillin,\(^9\) 1.2 million IU by intramuscular injection, daily for 10 consecutive days

Alternative regimen for penicillin-allergic non-pregnant patients

- doxycycline, 100 mg orally, twice daily for 14 days
  OR
- tetracycline, 500 mg orally, 4 times daily for 14 days

Alternative regimen for penicillin-allergic pregnant patients

- erythromycin, 500 mg orally, 4 times daily for 14 days

LATE LATENT SYphilis

(infection of more than two years’ duration without evidence of treponemal infection)

Recommended regimen

- benzathine benzylpenicillin, 2.4 million IU by intramuscular injection, once weekly for 3 consecutive weeks

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\(^8\) Benzathine benzylpenicillin synonyms: benzathine penicillin G; benzylpenicillin benzathine; benzathine penicillin.

\(^9\) Procaine benzylpenicillin synonyms: procaine penicillin G.
Alternative regimen
- procaine benzylpenicillin, 1.2 million IU by intramuscular injection, once daily for 20 consecutive days

Alternative regimen for penicillin-allergic non-pregnant patients
- doxycycline, 100 mg orally, twice daily for 30 days
  OR
- tetracycline, 500 mg orally, 4 times daily for 30 days

Alternative regimen for penicillin-allergic pregnant patients
- erythromycin, 500 mg orally, 4 times daily for 30 days

NEUROSYPHILIS

Recommended regimen
- aqueous benzylpenicillin,\(^\text{10}\) 12–24 million IU by intravenous injection, administered daily in doses of 2–4 million IU, every 4 hours for 14 days

Alternative regimen
- procaine benzylpenicillin, 1.2 million IU by intramuscular injection, once daily, and probenecid, 500 mg orally, 4 times daily, both for 10–14 days

This regimen should be used only for patients whose outpatient compliance can be assured.

Note
- Some authorities recommend adding benzathine benzylpenicillin, 2.4 million IU by intramuscular injection, in 3 consecutive doses once weekly, after completing these regimen, but there are no data to support this approach. Benzathine benzylpenicillin, 2.4 million IU by intramuscular injection does not give adequate therapeutic levels in the CSF.

\(^\text{10}\) Aqueous benzylpenicillin synonyms: benzylpenicillin potassium; benzylpenicillin sodium; crystalline penicillin, penicillin G potassium; penicillin G sodium.
Alternative regimen for penicillin-allergic non-pregnant patients

- doxycycline, 200 mg orally, twice daily for 30 days

OR

- tetracycline, 500 mg orally, 4 times daily for 30 days

**Note**

- The above alternatives to penicillin for the treatment of neurosyphilis have not been evaluated in systematic studies. Although their efficacy is not yet well documented, third-generation cephalosporins may be useful in the treatment of neurosyphilis.

- The central nervous system may be involved during any stage of syphilis. Clinical evidence of neurological involvement (e.g. optic or auditory symptoms, or cranial nerve palsies) warrants examination of the CSF. However, examination of the CSF is also highly desirable in all patients with syphilis of more than two years’ duration, or of uncertain duration, in order to evaluate the possible presence of asymptomatic neurosyphilis. Some experts recommend consulting a neurologist when caring for a patient with neurosyphilis. Careful follow-up is essential.

**CONGENITAL SYPHILIS**

**A. Early congenital syphilis (up to 2 years of age)**

**AND**

**Infants with abnormal CSF**

**Recommended regimen**

- aqueous benzylpenicillin 100 000–150 000 IU/kg/day administered as 50 000 IU/kg/dose IV every 12 hours, during the first 7 days of life and every 8 hours thereafter for a total of 10 days

OR

- procaine benzylpenicillin, 50 000 IU/kg by intramuscular injection, as a single daily dose for 10 days

**Note**

- Some experts treat all infants with congenital syphilis as if the CSF findings were abnormal. Antimicrobials other than penicillin (e.g. erythromycin) are not...
recommended for congenital syphilis except in cases of allergy to penicillin. Tetracyclines should not be used in young children.

B. Congenital syphilis of 2 or more years

Recommended regimen

- aqueous benzylpenicillin, 200 000–300 000 IU/kg/day by intravenous or intramuscular injection, administered as 50 000 IU/kg/dose every 4–6 hours for 10–14 days

Alternative regimen for penicillin-allergic patients, after the first month of life

- erythromycin, 7.5–12.5 mg/kg orally, 4 times daily for 30 days

3.5. CHANCROID

The causative organism is a Gram-negative facultative anaerobic bacillus, *H. ducreyi*. The infection is common in several parts of the world including Africa, the Caribbean and south-east Asia. Owing to widespread antimicrobial resistance in all geographical areas, tetracyclines and penicillins are not recommended for treatment of chancroid. To enhance compliance, single-dose treatments with effective antibiotics are preferred.

Management of lesions

No special treatment is required. Ulcerative lesions should be kept clean. Fluctuant lymph nodes should be aspirated as required through the surrounding healthy skin. Incision and drainage or excision of nodes may delay healing and is not recommended.

Follow-up

All patients should be followed up until there is clear evidence of improvement or cure. In patients infected with HIV, treatment may appear to be less effective, but this may be a result of coinfection with genital herpes or syphilis. Since chancroid and HIV infection are closely associated, and therapeutic failure is likely to be seen with increasing frequency, patients should be followed up weekly until there is clear evidence of improvement.