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MANAGEMENT OF SPECIFIC INFECTIONS

European guideline for the management of syphilis

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INTRODUCTION

Syphilis is classified as acquired or congenital. Acquired syphilis is divided into early and late syphilis. Early syphilis: primary, secondary and early latent (Centers for Disease Control [CDC]: acquired <1 year previously[1]; World Health Organization [WHO]: acquired <2 years previously[2]). Late syphilis: late latent (CDC: acquired $\geqslant 1$ year previously[1]; WHO: acquired $\geqslant 2$ years previously[2]), tertiary, including gummatous, cardiovascular and neurosyphilis (the latter two are also sometimes classified as quartenary syphilis). Congenital syphilis is divided into early (first 2 years of life) and late (apparent later in life), which includes the stigmata of congenital syphilis.

DIAGNOSIS

Clinical features

Incubation period: 10–90 days before a chancre (primary syphilis) develops, in symptomatic patients. Secondary syphilis develops 3–6 weeks after the appearance of the chancre.

Primary syphilis: an ulcer (chancre), usually with regional lymphadenopathy. The ulcer is single, painless and indurated with a clean base, discharging clear serum, in the anogenital region. Occasionally it may be atypical: multiple, painful, purulent, destructive, extragenital (including syphilitic balanitis of Follmann[3]). Any anogenital ulcer is syphilitic unless proven otherwise.

Secondary syphilis: multisystem involvement due to bacteraemia, which may recur up into the second year after infection. Generalized non-itchy polymorphic rash often affecting the palms and soles, condylomata lata, mucocutaneous lesions, generalized lymphadenopathy. Less commonly patchy alopecia, anterior uveitis (i.e. ocular syphilis, which may also cause scleritis, iritis, retinitis, papillitis, optic neuritis), meningitis, cranial nerve palsies, hepatitis, splenomegaly, periostitis and glomerulonephritis. The rash may be itchy, particularly in dark-skinned patients[4].

Latent syphilis: positive serological tests for syphilis with no clinical evidence of treponemal infection. Arbitrarily classified as early if acquired <1 year previously and late if acquired $\geqslant 1$ year previously.

Late syphilis includes:

- Gummatous syphilis: typical nodules/plaques or ulcers
- Neurosyphilis: meningovascular, parenchymatous (general paresis, tabes dorsalis), asymptomatic (abnormal cerebrospinal fluid (CSF))
- Cardiovascular syphilis: aortitis (asymptomatic), angina, aortic regurgitation, coronary ostia stenosis[5], aortic aneurysm (mainly thoracic).

Laboratory

Treponema pallidum from lesions or infected lymph nodes in early syphilis, demonstrated by:

- Darkfield microscopy
- Direct fluorescent antibody test—for oral or other lesions where contamination with commensal treponemes is likely
- Polymerase chain reaction (PCR)[6,7].

Serological tests for syphilis include[8,9]:

- Reaginic tests (cardiolipin/non-treponemal tests): Venereal Disease Research Laboratory test (VDRL), rapid plasma reagin test (RPR) and variants
- Specific tests (treponemal tests): *T. pallidum* haemagglutination assay (TPHA), micro-haemagglutination assay for *T. pallidum* (MHA-TP), *T. pallidum* particle agglutination test (TPPA), fluorescent treponemal antibody absorption test (FTA-abs test), treponemal enzyme immunoassay (EIA)/IgG (e.g. Captia), IgG immunoblot test for *T. pallidum*
- Specific anti-*T. pallidum* IgM antibody tests: 19S-IgM-FTA-abs test, IgM-immunoblot for *T. pallidum*, anti-*T. pallidum* IgM-antibody test using the EIA method (Captia EIA). Present indication for IgM antibody test screening for congenital syphilis and recent infection.

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Preliminary screening tests[10,11]:

- TPHA, MHA-TP or TPPA are the best single screening tests. VDRL or RPR are sometimes also performed (in addition)
- EIA/IgG-test is an alternative screening test
- FTA-abs test or EIA-IgM may be the first test to be positive if primary syphilis is suspected; the first test is reactive in 70–90% of cases[8].

Confirmatory tests if any screening test is positive[10,11]:

- Treponemal EIA, FTA-abs test (i.e. another treponemal test, e.g. TPHA if EIA is used for screening, EIA if TPHA is used for screening)
- IgG-immunoblot for *T. pallidum* if suspected false-positive TPHA/MHA-TP and/or FTA-abs test
- Always repeat positive tests to confirm results.

Test for serological activity of syphilis and for monitoring the effect of treatment:

- VDRL-test or RPR-test (or variants, i.e. other cardiolipin/non-treponemal tests).

Laboratory: false-negative syphilis serology[8,9]

- A false-negative reaginic (cardiolipin) test may occur in secondary syphilis due to the prozone phenomenon from using undiluted serum
- A temporary negative reaginic (cardiolipin) test has occasionally been reported in secondary syphilis and in patients with concomitant HIV infection (reactive on subsequent testing).

Laboratory: false-positive syphilis serology[8,9]

- Biological false-positive (BFP) reaginic (cardiolipin/non-treponemal) tests can be divided as acute (<6 months) and chronic ($\geqslant 6$ months). Acute BFP may be seen in pregnancy, post-immunization, recent myocardial infarction and in many febrile infective illnesses. Chronic BFP may be seen in injecting drug users, autoimmune diseases, leprosy, chronic liver pathology and old age. Occasional biological false-positive treponemal tests (FTA-abs test more than TPHA/MHA-TP) may be seen in autoimmune diseases, HIV infection and during pregnancy and can be excluded with the IgG immunoblot test for *T. pallidum*
- False positive syphilis serology (treponemal and cardiolipin/non-treponemal) is also found in endemic treponematoses and borreliosis. The treponematoses are caused by bacteria from the group of spirochaetes, which include Borrelia, Spirochaeta, Leptospira, Cristispira and Treponema, such as:
  - *T. pallidum* (venereal syphilis and endemic syphilis)
  - *T. pertenue* ('yaws'/framboesia tropica)
  - *T. carateum* (pinta)

  The antibodies to endemic treponematoses such as endemic syphilis, framboesia (yaws) and pinta cannot be distinguished from the antibodies induced by *T. pallidum*. A person with positive syphilis serology from a country with endemic treponematoses should be investigated and treated as for syphilis as a precautionary measure, unless previously adequately treated for syphilis
- The false-positive syphilis serology caused by the spirochaete *Borrelia burgdorferi* results from the antigenic relationship between *T. pallidum* and *B. burgdorferi*, since both are spirochaetes. This can usually be avoided by routine pre-incubation with *T. phagedenis*. False-positive treponemal reactions frequently occur however with the FTA-abs test. Now that the genome of *T. pallidum* has been mapped completely[12], new more specific test for *T. pallidum* may be developed
- False-positive syphilis serology in pregnancy:
  - False-positive cardiolipin/non-treponemal and treponemal reactions can occur in pregnancy, with treponemal tests the FTA-abs test is the one which may be false-positive
  - If a pregnant woman has been adequately treated for syphilis prior to the current pregnancy, there are no rational arguments for a so-called safety treatment. But in the case of a possible new syphilitic infection (recheck sexual partner) and also if there is any doubt about the adequacy of previous therapy, one should not hesitate to proceed with treatment.

Laboratory tests to confirm or exclude neurosyphilis[1,13,14]

- Lumbar puncture for examination of CSF is indicated in patients with[1,14]:
  - Clinical evidence of neurological involvement
  - Ocular, cardiovascular or gummatous syphilis
  - Concomitant HIV infection

  Note: Lumbar puncture for CSF examination is an option in non-HIV-infected patients with late latent syphilis or in whom the duration of latent syphilis infection is unknown. This examination should exclude asymptomatic neurosyphilis, although the benefit may be marginal[15] and the need minimal, as the risk of developing symptomatic neurosyphilis after standard parenteral treatment appears to be small in such patients[14,16–18], although it has been described[18].
- Examination of CSF: TPHA/MHA-TP/TPPA (qualitatively), FTA-abs test (qualitatively), VDRL test (quantitatively), total protein,

albumin level, number of mononuclear cells. Quantitative TPHA/MHA-TP and measurement of IgG and IgM level in CSF can also be performed, together with measurement of albumin, IgG and IgM level in serum

- Extra parameters in CSF: IgG-index, IgM-index, albumin quotient. The IgG-index decreases after adequate therapy, but may remain abnormal, as does the TPHA-index and the albumin quotient. IgM-index and the number of mononuclear cells in the CSF should become negative or normal within 1–2 years. The VDRL test in CSF may or may not become negative following therapy. The use of the different TPHA-indexes and ITpA-indexes has been controversial[13,19]. The value of the PCR for determination of the presence of *T. pallidum* antigen(s) in CSF and diagnosis of neurosyphilis is rather disappointing[13,14].

  —IgG-index (parameter for intrathecal IgG synthesis, normal value: <0.70)[13,18]:

$$\frac{\text{IgG level (mg/l) in CSF}}{\text{IgG level (mg/l) in serum}} : \frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}}$$

  —IgM-index (parameter for intrathecal IgM synthesis, normal value: <0.07)[18,19]:

$$\frac{\text{IgM level (mg/l) in CSF}}{\text{IgM level (mg/l) in serum}} : \frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}}$$

  — Albumin-quotient (parameter for disturbance of blood–brain barrier, normal value: <7.8)[13,18,19]:

$$\frac{\text{albumin level (mg/l) in CSF}}{\text{albumin level (mg/l) in serum}} \times 1000$$

  — TPHA-index, according to Luger[13] (parameter for intrathecal synthesis of anti-*T. pallidum*-specific IgG). This TPHA-index was shown to have a specificity of 100% and a sensitivity of 98.3% in one study involving 60 HIV-seronegative symptomatic neurosyphilis patients and controls[13]. This leaves the question of reproducibility of the CSF-TPHA (appears to be good), the sensitivity of the index in oligo- and asymptomatic neurosyphilis and the influence of HIV-infection. Confirmation of the findings of Luger *et al*. has been limited so far[13].

$$\frac{\text{CSF-TPHA titre}}{\text{Albumin quotient}}$$

- Criteria for the diagnosis of neurosyphilis[13,14]:

TPHA/MHA-TP and/or FTA-abs test positive (in CSF)
and
Increased number of mononuclear cells ($>10/mm^3$ in CSF)
plus
IgG-index $\geqslant 0.70$ and/or IgM-index $\geqslant 0.10$ (in CSF)
or
positive VDRL test (in CSF).

- Additional criteria in HIV-seronegative patients suspected of symptomatic neurosyphilis: TPHA-index (according to Luger, see above) >70 and <500: compatible with neurosyphilis; TPHA-index (according to Luger, see above) >500: definite neurosyphilis[13]
- Other considerations:
  — Finding in CSF a positive TPHA, an increased number of mononuclear cells and a raised IgG- and/or IgM-index only provides circumstantial evidence for the diagnosis of neurosyphilis. A positive VDRL test in CSF is seen as more direct evidence of neurosyphilis
  — The number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (tabes dorsalis, general paresis)[18,19]
  — The VDRL test in CSF can be negative in neurosyphilis[13,18,19]
  — A positive TPHA/MHA-TP/TPPA or FTA-abs test in CSF by itself does not confirm the diagnosis of neurosyphilis, but a negative treponemal CSF test excludes neurosyphilis[13]
  — Tests may be performed for the presence of HIV-RNA or HIV-p24 Ag in CSF of HIV-infected individuals, which indicate HIV-infection of the central nervous system
  — The criteria outlined above have not generally been validated in HIV-seropositive patients.

Screening test to exclude symptomatic cardiovascular syphilis

- Chest radiograph

Investigation for ocular syphilis

- Indicated if ocular complaints are present
  Note: Ocular assessment (slit lamp) may be helpful to differentiate between acquired or congenital ocular syphilis (interstitial keratitis) in cases of latent infection of uncertain duration.

MANAGEMENT[5,14,16,20]

General

- 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 treponemicidal, but is substantially lower than the maximally effective *in vitro* level of concentration, which is far higher (0.36 mg/l)[5,16]

- Duration of treponemicidal level of antimicrobial should be at least 7–10 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[5]. Longer duration of treatment is needed as the duration of infection increases (more relapses were seen in that stage after short courses of treatment), possibly because of more slowly dividing treponemes in late syphilis. Treponemes have shown to persist despite apparently successful treatment[20]. The significance of this finding, if any, is unknown
- Long-acting benzathine penicillin 2.4 million units provides a treponemicidal penicillinaemia for up to 3–4 weeks (21–23 days)[5,21]. With daily parenteral treatment with procaine penicillin a 'safety margin' is provided by giving courses lasting 10–14 days in early syphilis and 10–21 days in late syphilis. However, well controlled clinical data are lacking on the optimal dose, duration of treatment and long-term efficacy of antimicrobials, even of penicillin, which has been used most extensively[16]
- The recommendations are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinion, case studies and past clinical experience[16]
- Parenteral rather than oral penicillin treatment has generally been the treatment of choice because parenteral therapy is supervised with guaranteed bioavailability. Oral fenoxymethylpenicilline is an option however[22], and amoxicillin given orally in combination with probenecid resulted in treponemicidal CSF penicillin levels[23,24]
- Non-penicillin antibiotics that have been evaluated are tetracyclines, including doxycycline, which is the preferred tetracycline with penetration into the CSF[16,20,25], and erythromycin, all taken orally. Erythromycin is least effective and does not penetrate the blood–brain or placental barriers well[20]. Newer antitreponemal regimens include oral azithromycin[16,26–28] and intramuscular or intravenous ceftriaxone[29,30]. The latter has good CSF penetration. More data are required, however, before either can be generally recommended, although both may be preferable to erythromycin and tetracycline
- The host immune response is important as 60% of untreated patients go through life without developing late complications[31]. CSF involvement is common in early syphilis[32,33]. Although both benzathine penicillin and standard regimens of parenteral procaine penicillin do not achieve treponemicidal CSF levels[14,16,34,35] the prevalence of late syphilis, including neurosyphilis, remains low, indicating that treatment is effective and suggesting that host immune responses in early syphilis play an essential part. However, standard treatment with parenteral benzathine penicillin has been associated with failure in pregnant women[36–38]
- Benzathine penicillin is available as Penidural® and is widely used because of ease of treatment. Using lidocaine solution as part of the solvent reduces the pain associated with injection and may improve compliance. Compliance with daily intramuscular injections with procaine penicillin has been good in the UK[39]. Although both penicillins appear to be effective in the parenteral regimens used for early and late syphilis, these regimens have not yet been comparatively studied[16]. Nor has parenteral procaine penicillin plus oral probenecid been compared with intravenous penicillin in the treatment of neurosyphilis. The optimal treatment schedule for syphilis in pregnant women is not known. The exact value of the serum titre response of cardiolipin/nontreponemal tests has never been fully elucidated; universally accepted standards for cure or failure using the serological response do not exist. The control of syphilis over the past 50 years has been excellent, however, compared to the pre-penicillin age. Late complications of syphilis and/or failures of treatment are uncommon, even in patients with concomitant HIV infection, indicating that the treatment schedules presently used seem fairly adequate, although there remains a need for properly controlled studies
- The risk of a syphilis patient with a concomitant HIV infection of developing a more aggressive course with (early) neurosyphilis, ocular syphilis, treatment failure and relapse appears to be slightly increased[1,14,16,40]. Consequences thereof: (a) HIV-antibody test should always be offered to patients with syphilis of any stage not yet adequately treated, as the HIV-status may affect the policy for diagnosis, follow-up and rarely of treatment; (b) careful follow-up of syphilis patients with concomitant HIV-infection, including CSF examination 2 years after treatment of early syphilis and at the initial diagnostic stage of an HIV-infected patient with late latent syphilis or latent syphilis of unknown duration
- The Russian Federation has devised regularly updated treatment recommendations, lastly from 1999 (see Appendix). These carefully worked-out recommendations often differ from those issued in other European countries and the USA. The vast experience in the Russian Federation does therefore not provide other countries with answers, due to differences of dosage and duration of commonly used antibiotics.

Early syphilis (primary, secondary and early latent acquired <1 year previously), recommended regimen[1,14,16,41-45]

First-line therapy options:

- Benzathine penicillin (Penidural®) 2.4 million units intramuscularly (IM) (each buttock 1.2 million units) on day 1[1,5,41,42,44,45]. Using lidocaine solution as part of the solvent reduces the discomfort associated with injection
- Procaine penicillin 600 000 units IM daily for 10–14 days[5,41,42,46]. If unable to give daily procaine penicillin on the weekend, one may give long-acting Biclinocillin (benethamine penicillin 1 million units) 1.67 million units IM on Friday to cover the weekend[42]. Some physicians recommend a larger dose of procaine penicillin (1.2 million units)[41], certainly for heavier patients (e.g. 80–100 kg)
- Benzyl penicillin 1 million units IM daily for 10–14 days[44].

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) for 14 days[1,16,20,25]
- Tetracycline 500 mg four times daily for 14 days[1,16,20]
- Erythromycin 500 mg four times daily for 14 days[16,20]
- Other options: azithromycin 500 mg once daily for 10 days[16,26–28], ceftriaxone 250–500 mg IM once daily for 10 days[29,30].

Late latent (acquired ⩾1 year previously or of unknown duration), cardiovascular and gummatous syphilis, recommended regimen

First-line therapy options:

- Benzathine penicillin (Penidural®) 2.4 million units IM (each buttock 1.2 million units) weekly on day 1, 8 and 15[1,41,43–45]. Reconstitution of benzathine penicillin with lidocaine reduces the discomfort associated with injection
- Procaine penicillin 600 000 units IM daily for 17–21 days[41,43]. If unable to give daily procaine penicillin on the weekend, one may give long-acting Biclinocillin (benethamine penicillin 1 million units) 1.67 million units IM on Friday to cover the weekend[42]. Some physicians recommend a larger dose of procaine penicillin (1.2 million units)[41], certainly for heavier patients (e.g. 80–100 kg)
- Benzyl penicillin 1 million units IM daily for 21 days[44].

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) for 21–28 days[1,20,25,41,43-45]
- Tetracycline 500 mg 4 times daily for 28 days[1]
- Erythromycin 500 mg 4 times daily 28 days[20].

Neurosyphilis and ocular syphilis, recommended regimen

- Biological plausibility suggests that regimens that achieve treponemicidal levels of an antibiotic in CSF should be the treatment of choice. Options are intravenous (IV) or parenteral (IM)/oral therapy using probenecid. Data comparing these two options are lacking
- There are conflicting data over the effectiveness of producing a treponemicidal CSF penicillin level using the procaine penicillin/probenecid combination[20,47,48]. Concern that the CSF penicillin level is increased at the expense of the central nervous system (CNS) tissue level[47,49] may not be relevant, because the levels in both CSF and CNS tissue are in fact higher with probenecid than without, with a relatively much higher level in the CSF[20]. The experience in the UK with treatment of neurosyphilis with the procaine penicillin/probenecid combination has been positive so far. The availability of probenecid may be a problem however
- In ocular syphilis, also in uveitis syphilitica of short duration, effective treatment can be realized with parenteral benzathine penicillin[50,51], but in patients with serious ocular involvement (cave: ocular syphilis is often associated with (a)symptomatic neurosyphilis), or ocular involvement of longer duration (with threat of permanent loss of vision), treatment as for neurosyphilis should be preferred.

First-line therapy:

- Benzyl penicillin 12–24 million units IV daily, as 2–4 million units every 4 hours for 10–21 days[1,41,43,44]
- Benzyl penicillin 0.15 million units/kg/day IV, spread over 6 doses (every 4 hours) for 10–14 days[45,49]
- Procaine penicillin 1.2–2.4 million units IM daily PLUS probenecid 500 mg orally 4 times daily, both for 10–21 days[1,41,43].

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg twice daily for 28–30 days[25,41,43,45].

Follow up

Repeat CSF examination should be performed not earlier than 1–2 years after treatment of neurosyphilis, unless clinical deterioration occurs. If performed earlier, e.g. at 3 or 6 months, non-relevant CSF findings suggesting aggravation due to the so-called paradoxical response may cause unnecessary confusion[52]. In meningovascular

neurosyphilis the number of mononuclear cells in CSF generally normalizes faster (within 6–12 months) than in parenchymatous neurosyphilis (within 1–2 years). As has been stated above, the number of mononuclear cells in CSF and the IgM-index should become normal within 1–2 years, while albumin quotient, IgG-index and TPHA-index may remain abnormal and the CSF-VDRL-test positive.

SPECIAL SITUATIONS

Pregnancy

In pregnant women with untreated early syphilis, 70–100% of infants will be infected, with stillbirths in up to one-third of cases. Standard treatment has been used with good results, but because of some reports of insufficient response in mother and infant, more aggressive treatment has been advocated[1,16,36–38].

First-line options for treatment of early syphilis (acquired <2 years previously):

- Benzathine penicillin (Penidural®) 2.4 million units IM (each buttock 1.2 million units) weekly on days 1 and 8[1]
- Procaine penicillin 600 000 or 1.2 million units IM daily for 10–14 days[42].

Penicillin allergy:

- Desensitization to penicillin may be considered followed by first-line treatment[1]
- Alternative options:
  - Azithromycin, 500 mg once daily for 10 days, which has been used for chlamydial infection in pregnant women as reported in a Cochrane analysis[53]. Published evidence of safety of use during pregnancy is limited however
  - Ceftriaxone, 250–500 mg IM daily for 10 days, may also be given during pregnancy[54]. Published evidence of safety of use during pregnancy is limited however
  - Consideration might be given on re-treating mothers with doxycycline after delivery.

Prevention of congenital syphilis by serological screening during pregnancy and preventive neonatal treatment:

- Serological screening is recommended in the USA at: (a) initial pregnancy control; (b) 28 weeks of gestation; (c) delivery, if high-risk for congenital syphilis[1]. In The Russian Federation it is recommended at: (a) initial pregnancy control; (b) 21 weeks of gestation; (c) 36 weeks of gestation. Each country should decide on its own screening policy, if possible based on a cost-effectiveness analysis
- All infants born to sero-positive mothers should be treated with a single dose of benzathine penicillin 50 000 units/kg IM, whether or not the mother was treated during pregnancy, especially in high-prevalence countries[1,41].

Congenital syphilis

Diagnosis

Confirmed congenital infection:

- *T. pallidum* demonstrated by dark-field microscopy, immunofluorescent microscopy, PCR or specific staining of specimens for histopathological examination, e.g. from skin lesions, navel, placenta or autopsy material[14].

Presumed congenital infection[1,42,55]:

- A stillborn neonate with a positive treponemal test for syphilis
- Children with a positive treponemal test for syphilis in combination with one of the following:
  - Persistent rhinitis, condylomata lata, osteitis, periostitis, osteochondritis, ascites, cutaneous and mucous membrane lesions, hepatitis, hepatosplenomegaly, glomerulonephritis, haemolytic anaemia
  - Radiological abnormalities of the long bones suggestive of congenital syphilis
  - A positive VDRL test in CSF
  - A 4-fold increase or more of the TPHA/MHA-TP titre in the child's as opposed to the mother's serum (both obtained simultaneously at birth)
  - A 4-fold increase or more of the titre of a cardiolipin/non-treponemal test in the child's as opposed to the mother's serum (both obtained simultaneously at birth)
  - A 4-fold increase or more of the titre of a cardiolipin/non-treponemal test within 3 months after birth
  - A positive 19S-IgM-FTA-abs test, EIA-IgM and/or IgM-immunoblot for *T. pallidum* in the child's serum
  - A mother, in whom syphilis was confirmed during pregnancy, but who was not adequately treated either before or during pregnancy
- A child >12 months-of-age with a positive treponemal serological test for syphilis.

Late congenital syphilis 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

- Serological tests can be negative in infants infected in late pregnancy and should be repeated. When the mother is treated during the last trimester of pregnancy, the treatment can be inadequate for the child and the child may still develop congenital syphilis.

Investigations

- VDRL, TPHA/MHA-TP (quantitative), anti-treponemal IgM (19S-IgM-FTA-abs test and/or IgM-immunoblot or EIA-IgM) from infant's blood and not umbilical cord blood, because false-positive and -negative tests may result[55]
- Blood: full blood count, liver function, electrolytes, albumin, IgG, IgM
- CSF: cells, albumin, IgG, IgM, TPHA, VDRL
- X-rays of long bones
- Ophthalmic assessment as indicated.

Treatment options

- Benzyl penicillin 150 000 units/kg IV daily (administered in 6 doses every 4 hours) for 10–14 days[1,41,44]
- Procaine penicillin 50 000 units/kg IM daily for 10–14 days[1,41,42]
- If CSF is normal: benzathine penicillin 50 000 units/kg IM (single dose)[1,41].

HIV-infected patients

General remarks

- Serological tests for syphilis in patients with HIV co-infection are generally reliable for the diagnosis of syphilis and for evaluation of treatment response
- False-negative and -positive tests and delayed appearance of seroreactivity have been reported[1,14,16]
- In HIV-infected individuals with clinical suspicion of syphilis and (repeatedly) negative syphilis serology, it is advisable to perform other diagnostic tests apart from the preliminary screening test, e.g. histological, immunofluorescent or PCR examination of a biopsy from a clinically suspected lesion and direct dark-field microscopy of the exudate of early syphilitic lesions for spirochaetes
- HIV-infected patients with early syphilis appear to have a slightly increased risk of (early) neurological and ocular involvement and higher rate of treatment failure with benzathine penicillin including more frequent serological relapse[1,14,16,40]. Therefore careful follow-up is essential
- CSF examination is advisable[1,14,16]:
  - — As part of the initial diagnostic programme in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration (see earlier in the text)
  - — 2 years after treatment of early syphilis (not advised for non-HIV infected patients).

Treatment of syphilis in patients with concomitant HIV infection

- Treatment should be given as for non-HIV-infected patients.

Note (1): Careful follow-up is essential (see above and at follow-up).

Note (2): In the UK, where neurosyphilis is often treated with procaine penicillin IM plus probenecid orally, which regimen can be given on an outpatient basis, it has been suggested that HIV-infected syphilis patients should be treated with the procaine regimen mentioned, to prevent the development of neurological involvement. Hard evidence for this policy is lacking, however[42,43].

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, resolving within 24 hours
- 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
- Uncommon in late syphilis, but can potentially be life-threatening if involvement of strategic sites (e.g. coronary ostia, larynx, nervous system)
- Prednisolone can abolish the febrile episode[56], but is unproven in ameliorating 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 *per se*, biological plausibility would suggest that it may help
- Systemic treatment with a blocker of tumour necrosis factor (TNF) may be more effective than systemic treatment with a corticosteroid[57]
- Management:
  - — If cardiovascular or neurological involvement (including optic neuritis) exists, in-patient management is advisable
  - — Prednisolone 10–20 mg 3 times daily for 3 days, starting anti-treponemal treatment after 24 hours of commencing prednisolone
  - — Antipyretics.

Procaine reaction (procaine psychosis, procaine mania, Hoigné syndrome)

- Due to inadvertent intravenous injection of procaine penicillin; may be minimized by the 'aspiration technique' of injection

- Characterized by fear of impending death, may cause hallucinations or fits immediately after injection. Lasts less than 20 minutes
- Management:
  - — Exclude anaphylaxis
  - — Calm and verbal reassurance: restraint may be necessary
  - — Diazepam rectally/IV/IM if convulsions.

Anaphylactic shock

- Facilities for treatment of anaphylaxis should be available as penicillin is one of the commonest causes
- Management:
  - — Epinephrine (adrenaline) 1:1000 IM 0.5 ml, followed by:
  - — IM/IV antihistamine, e.g. chlorpheniramine 10 mg
  - — IM/IV hydrocortisone 100 mg.

MANAGEMENT OF PARTNERS

- All patients with syphilis should be seen for partner notification (notification by the patient = patient referral, by a health department = provider referral), health education, STD prevention and confirmation of any past treatment history
- Although the division of latent syphilis in early and late stages has been useful for treatment and partner notification, this classification can be problematic for use in surveillance, as a substantial number of late, hypothetically non-infectious, latent syphilis cases (latent syphilis of unknown duration was classified as late latent) turned out to be probable early, infectious, latent syphilis according to one report[14]
- Secondary syphilis relapse can occur within the first 2 years of infection, and syphilis is thought to be infectious through intercourse for up to 2 years after acquisition
- Partner notification assists community efforts to reduce the disease burden, fulfils ethical obligations to warn the unsuspecting and, probably not unimportant, can delineate the risk networks hosting transmission. Partner notification programmes may have poor results though, which poses a problem because syphilis may cause serious morbidity[14]
- For patients with primary syphilis, sexual partners within the past 3 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, including pregnant women, of patients with early syphilis are likely to be infected
- Immediate epidemiological treatment for sexual partners should be considered (especially of pregnant partners), unless partners are able to attend regularly for exclusion of syphilis through clinical and serological examination
- Serological tests for syphilis should be performed at the first visit and repeated at 6 weeks and 3 months
- Notification of syphilis to the relevant authority is required in many European countries, particularly early syphilis and congenital syphilis.

FOLLOW UP

The follow up to ascertain cure and detect reinfection or relapse is achieved by assessing the clinical and serological response.

- For early syphilis, minimum clinical and serological (cardiolipin/non-treponemal tests: VDRL or RPR) assessment according to the following follow-up scheme might be used: monthly during the first 3 months after treatment, then at 6 and 12 months. Follow-up of HIV-infected patients treated for early syphilis should be more frequent, e.g. at 1, 2, 3, 6, 9, 12, 18 and 24 months[1,42], and may be ended by CSF examination[14]
  - — After treatment of early syphilis the titre of cardiolipin/non-treponemal tests (e.g. VDRL and/or RPR) should decline by 2 dilution steps (4-fold) within 6 months (within 1 year for HIV-positive patients)[1].
  - — If this does not occur, should additional treatment be given (according to the CDC[1]: benzathine penicillin 2.4 million units IM on day 1, 8 and 15)? If the clinical response has been adequate, one might decide against additional treatment. If the clinical response was inadequate or impossible to monitor as in latent syphilis, one might decide in favour of additional treatment
- In late (latent) syphilis the serological response of cardiolipin/non-treponemal tests is often absent. In non-HIV-infected late latent syphilis patients with a reactive cardiolipin/non-treponemal test, which remains stable in the lowest titre range, follow-up after treatment is generally not indicated
- Early clinical relapse tends to occur in the oral and anal regions
- An increase of >2 dilution steps (4-fold) in a cardiolipin/non-treponemal test suggests reinfection or reactivation
- Follow-up examination of CSF should be performed 1–2 years after treatment of neurosyphilis
- Specific treponemal tests may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary re-treatment

- Reinfection or relapse should be re-treated preferably with supervised treatment schedules to ensure compliance, and sexual partners should be rescreened.

APPENDIX

Syphilis treatment recommendations for the Russian Federation, formulated by the Central Research Institute for Skin and Venereal Disease, Moscow, approved by the Ministry of Health

Introduction

The management of syphilis in the former USSR was always strictly regulated. The first regulations were published in the USSR in 1948. Those regulations concerned both diagnosis and treatment of the disease. Since 1948 the regulations have been updated several times. The epidemic of syphilis that occurred in the Russian Federation during the last decade necessitated a change in the management of syphilis. Here, the last treatment regulations of 1999 are given.

Principles of syphilis management

1 Specific treatment: symptoms suggestive of syphilis, confirmed by positive laboratory tests
2 Preventive treatment: absence of clinical and laboratory abnormalities, but a history of sexual or other close physical contacts <2 months previously with a patient, then suffering from an early form of syphilis
3 Prophylactic treatment:
   (*a*) of a pregnant woman, who was treated for syphilis in the past, but still has positive serological tests
   (*b*) of a pregnant woman, who acquired syphilis during that pregnancy
   (*c*) of a newborn, from a woman who acquired syphilis during the pregnancy
4 Treatment *ex juvantibus*: no evident laboratory abnormalities, but patients have lesions in internal organs suspected to be due to syphilis
5 Syndromic treatment: clinical symptoms suggestive of syphilis without opportunity to perform confirmatory laboratory tests.

Serologic tests

Part of a separate statutory protocol, formulated by the Central Research Institute for Skin and Venereal Diseases, Moscow, approved and issued as a law early in 2001 by the Ministry of Health.

Primary screening tests (in 2001 the TPHA has been introduced as a primary screening test for a validation period of 2 years; in blood donors that test was already routinely used):

- Reaction of microprecipitation (RMP, i.e. VDRL test or rapid plasma reagin (RPR) test)

or

- Complex of serologic reactions (CSR) or TPHA or EIA.

Confirmation tests:

- TPHA or EIA or FTA-abs test or TPI

Complex of serologic reactions (CSR):

- Reaction of microprecipitation (RMP, i.e. VDRL test or RPR)

and

- Two complement-fixation reaction (CFR) tests using reaction of Wassermann (RW) with a cardiolipin and a treponemal antigen.

Follow-up tests (parameter of serologic response):

- RMP or CSR

Antibiotics (in alphabetical order) recommended for treatment of syphilis

1 Azithromycin
2 Ampicillin
3 Benzathine benzylpenicillin (dibenzylethylenediamine salt of penicillin, BBP) (Bicillin-1, Retarpen®, Extencillin®)
4 Bicillin-3 (combination of dibenzylethylenediamine, novocaine and sodium salts of penicillin in a rate of 1:1:1)
5 Bicillin-5 (combination of dibenzylethylenediamine and novocaine salts in a rate of 4:1)
6 Benzylpenicillin sodium salt (SBP)
7 Benzylpenicillin novocaine salt (NBP)
8 Ceftriaxone
9 Doxycycline
10 Erythromycin
11 Oxacillin
12 Procaine benzylpenicillin (PBP)
13 Tetracycline.

Preventive treatment

1 BBP (Extencillin®, Retarpen®, Bicillin-1) 2.4 million units IM once, Bicillin-3 1.8 million units or Bicillin-5 1.5 million units IM twice (within one week)
2 PBP 1.2 million units IM once daily or NBP 600 000 units IM twice daily for 7 days
3 In patients, who received seropositive blood from a donor: treatment as in primary syphilis if transfusion <3 months previously or serologic tests if transfusion $\geqslant 3$ months previously.

If contact with a syphilis patient was >2 months previously, serologic tests (CSR plus FTA-abs test) should be performed twice within a period of 2 months, if contact was >4 months previously, serologic tests (CSR plus FTA-abs test) should be performed once.

Management of primary syphilis

1 BBP (Extencillin®, Retarpen®) 2.4 million units IM twice with 7 days' interval (day 1 and 8) or Bicillin-1 2.4 million units IM thrice with 5 days' interval (day 1, 6 and 11)
2 Bicillin-3 1.8 million units IM or Bicillin-5 1.5 million units IM for a total of 5 doses given twice a week

3 PBP 1.2 million units IM daily for 10 days or NBP 600 000 units IM twice daily for 10 days
4 SBP 1 million IM 4 times daily (every 6 hours) for 10 days.

Management of secondary and early latent syphilis (<2 years previously acquired)

1 BBP (Extencillin®, Retarpen®) 2.4 million units IM thrice with 7 days' interval (day 1, 8 and 15) or Bicillin-1 2.4 million units IM 6 times with 5 days' interval (day 1, 6, 11, 16, 21 and 26)
2 Bicillin-3 1.8 million units IM or Bicillin-5 1.5 million units IM for a total of 10 doses given twice a week
3 PBP 1.2 million units IM daily for 10 days or NBP 600 000 units IM twice daily for 20 days
4 SBP 1 million units IM 4 times daily (every 6 hours) for 20 days.

The last two regimens (3 and 4) are recommended in early latent syphilis >6 months previously acquired and in secondary syphilis with leukoderma or alopecia.

Management of early visceral syphilis or early neurosyphilis

Definition of early visceral syphilis: specific involvement of internal organs during the early stage of syphilis (<2 years previously acquired).

Definition of early neurosyphilis: specific involvement of the central nervous system (meningovascular syphilis) in the first 3 years after infection.

Note: These patients must be treated as in-patients under the supervision of a physician.

(A) Therapy of early visceral syphilis:
1 SBP 1 million units IM four times daily for 20 days
2 NBP 600 000 units IM twice daily or PBP 1.2 million units IM once daily for 20 days

In all cases additional symptomatic therapy is recommended (e.g. systemic corticosteroids).

(B) Therapy of early neurosyphilis:
1 SBP 10 million units IV in 400 ml of isotonic solution twice daily during 1.5–2 hours of infusion for 14 days
2 SPB 2–4 million units IV 6 times daily for 14 days.

Management of tertiary and late latent syphilis (⩾2 years previously acquired)

Definition of tertiary syphilis: gummatous and/or tubercular cutaneous lesions with or without (cardiovascular and/or gummatous) visceral involvement.

In tertiary syphilis with cutaneous lesions with concomitant specific involvement of internal organs the recommended regimens are the same as in late visceral syphilis.

In tertiary syphilis with cutaneous lesions without visceral involvement and late latent syphilis the following regimens are recommended:

1 SBP 1 million units IM 4 times daily for 28 days, followed by the same course for 14 days after 2 weeks' interval
2 NBP 600 000 units IM twice daily for 28 days, followed by the same course for 14 days after 2 weeks' interval
3 PBP 1.2 million units IM once daily for 20 days, followed by the same course for 10 days after 2 weeks' interval.

Note on the use of PBP: a course of 28 days is recommended, as in late visceral syphilis, unless adverse reactions prevent prolongation of the course.

Management of late visceral syphilis and late neurosyphilis

Definition of late visceral syphilis: cardiovascular syphilis and/or gummatous involvement of internal organs.

Definition of late neurosyphilis: specific parenchymatous involvement of the central nervous system, i.e. tabes dorsalis, dementia paralytica, taboparalysis, primary atrophy of the optical nerve.

(A) Late visceral syphilis:
1 SBP 400 000 units IM 8 times daily for 28 days, followed by a second course for 14 days after 2 weeks' interval
2 NBP 600 000 units IM twice daily or PBP 1.2 million units IM once daily for 28 days, followed by a second course for 14 days after 2 weeks' interval.

Treatment should be initiated, before the first penicillin course, by 2 weeks of an oral broad spectrum antibiotic (tetracycline or erythromycin 4×500 mg a day).

(B) Late neurosyphilis: the recommended regimens are the same as in early neurosyphilis, but with an additional second course after 2 weeks interval.

Penicillin allergy: alternative regimens for the management of syphilis

1 Doxycycline 2×100 mg or tetracycline 4×500 mg orally for 10, 15 or 30 days (for preventive treatment, treatment of primary and secondary syphilis and treatment of early latent syphilis respectively)
2 Semisynthetic penicillines: oxacillin or ampicillin 1 g IM 4 times daily for 10, 14 or 28 days (for preventive treatment, treatment of primary or secondary syphilis and treatment of early latent syphilis respectively)
3 Ceftriaxone 250 mg IM once daily for 5 or 10 days (for preventive treatment and treatment of primary syphilis respectively), 500 mg IM once daily for 10 days (secondary and early latent

syphilis) or 1000–2000 mg IM once daily for 14 days (late latent and neurosyphilis).
4 Azithromycin 500 mg orally once daily for 10 days for early syphilis (primary, secondary and early latent syphilis).

Specific and prophylactic treatment in pregnancy
Specific treatment:

(A) Specific treatment of pregnant women before the 18th week of pregnancy is the same as in non-pregnant women
(B) For specific treatment after the 18th week of pregnancy the following regimens are recommended:
- Primary syphilis:
  1 PBP 1.2 million units IM daily or NBP 600 000 units IM twice daily for 10 days
  2 SBP 1 million units IM 4 times daily (every 6 hours) for 10 days
- Secondary and early latent syphilis:
  1 The same regimens as in primary syphilis, but for 20 days.

Prophylactic treatment of pregnant women, who have been treated for syphilis in the past, but are still seropositive:

(A) Treatment, the same regimen as for primary syphilis, is usually started after the 20th week of pregnancy.
(B) If specific treatment is given after the 18th week, that treatment should be followed by prophylactic treatment.

Alternative therapy in case of penicillin allergy: erythromycin or semisynthetic penicillins.

Management of syphilis in children
Prophylactic treatment of a newborn is indicated if the mother, seropositive at the time of labour, of a clinically asymptomatic newborn was not treated or treated too late (after the 32nd week of pregnancy):

(A) If the mother was not treated, the prophylactic regimen for the newborn is the same as in congenital syphilis
(B) If the mother was insufficiently treated or if she was still seropositive at labour after adequate treatment, the following regimens are recommended:
  1 SBP 100 000 units/kg/day IM 6 times daily for 10 days
  2 NBP 50 000 units/kg/day IM twice daily or PBP 50 000 units/kg/day IM once daily for 10 days
  3 BBP 50 000 units/kg twice with 7 days interval (day 1 and 8).

Specific treatment of a newborn with early congenital syphilis, symptomatic or asymptomatic:

(A) Newborn with normal CSF:
  1 SBP 100 000 units/kg/day IM 6 times daily for 14 days
  2 NBP 50 000 units/kg/day IM twice daily or PBP 50 000 units/kg/day IM once daily for 14 days
  3 BBP 50 000 units/kg/day thrice with 7 days interval (day 1, 8 and 15), provided the newborn is not <2 kg in weight
(B) Newborn with abnormal CSF or CSF not investigated:
  1 The same regimens as for (A), but BBP is not recommended

Penicillin allergy, alternative treatment:
1 Oxacillin or ampicillin or ceftriaxone (80 mg/kg/day for 14 days).

Specific treatment of late congenital syphilis:
1 PBP 50 000 units/kg/day IM once daily or NBP 50 000 units/kg/day IM twice daily for 28 days, followed by a second course for 14 days after 2 weeks' interval
2 SBP 50 000 units/kg/day IM 6 times daily for 28 days, followed by a second course for 14 days after 2 weeks' interval.

Clinico-serological follow up after treatment of syphilis
Follow up:
- After preventive treatment of adults and children and after treatment of primary syphilis: at 3 months
- After treatment of early forms of syphilis in patients with a positive CSR (RMP): until complete negativation and for 6 months thereafter
- After treatment of late forms of syphilis and after treatment of neurosyphilis: during 3 years (serum CSR every 6 months during 2nd and 3rd year after treatment, specific seroreactions once a year); after treatment of neurosyphilis: examination of CSF every 6 months during 3 years
- Seroresistant patients are followed during 3 years
- Newborns free from congenital syphilis, but born from mothers with syphilis, are followed during 1 year irrespective of prophylactic treatment.

Seroresistance and additional treatment:
- Seroresistance is defined as a persistently positive CSR >1 year after adequate specific treatment of early syphilis
- Delayed return to negative serology: decline in titre of reagins, at least 4-fold (2 steps), $\geqslant 1$ year after adequate specific treatment
- In such cases the following additional treatment regimens are recommended:
  1 SBP 1 million units IM 6 times daily for 20 days
  2 PBP 1.2 million units IM once daily or NBP 600 000 units IM twice daily for 20 days

3 BBP 2.4 million units IM thrice with 7 days' interval (day 1, 8 and 15)
4 Ceftriaxone 1000 mg IM daily for 10 days.

Prerequisites for cure:

- Administration of adequate treatment
- Normalization of clinical symptoms
- Normalization of serologic reaginic reactions and other relevant laboratory tests.

Removal of a patient from the register requires:

- Final complete serologic testing including, after neurosyphilis, CSF examination
- Specialist examination of organs previously involved with late syphilis, including (early) visceral syphilis and neurosyphilis.

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