2008 European Guideline on the Management of Syphilis

Date: 1st of December 2008
Proposed date of revision: June 2012

Authors:
Patrick French (Chair), Mikhail Gomberg, Michel Janier, Bruno Schmidt, Pieter van Voorst Vader, Hugh Young.

Guideline Editor
Dr Raj Patel MB CHB(Hons) FRCP

Address for Correspondence
Camden Primary Care Trust and University College London
The Mortimer Market Centre
Mortimer Market
London WC1E 6JB
UK

Declerations of Interest: none

Introduction

Syphilis is classified as acquired or congenital. Acquired syphilis is divided into early and late syphilis. Early syphilis: primary, secondary and early latent infection. The European Centre for Disease Prevention and Control (ECDC) defines early syphilis as syphilis acquired <1 year previously and the World Health Organisation (WHO) defines early syphilis as syphilis acquired <2 years previously.[1,2] Late syphilis: late latent and tertiary syphilis (gummatous, cardiovascular and neurosyphilis). The ECDC defines late syphilis as syphilis acquired >1 year previously, the WHO as syphilis acquired >2 years previously.[1,2] Congenital syphilis is divided into early (first 2 years of life) and late, including stigmata of congenital syphilis.

This guideline is an update of the European IUSTI Syphilis Guideline 2001.[3] Six scientific back-ground articles linked with this update are also available.[4,5,6,7,8,9]

Case finding

Routine tests for syphilis should be taken in all pregnant women or those people donating blood, and the following groups at higher risk of syphilis: all patients who are newly diagnosed with STI; persons with HIV; patients with hepatitis B; patients with hepatitis C; patients suspected of early neurosyphilis (i.e. unexplained sudden visual loss (uveitis), unexplained sudden deafness (otitis) or meningitis); patients who engage in sexual behaviour that puts them at risk (e.g. men who have sex with men, sex workers and all those individuals at higher risk of acquiring STIs).

Diagnosis

A. Clinical features and stage characteristics

Incubation period: 10-90 (usually 14-21 days) days before the ulcer (chancre) of primary syphilis develops. Secondary syphilis develops 3-6 weeks after the appearance of chancre.

Primary syphilis: an ulcer (chancre), usually with regional lymphadenopathy. The ulcer is usually single, painless and indurated with a clean base discharging clear serum and it is usually located in the ano-genital region. Occasionally it may be atypical, more so in HIV-infected patients: multiple, painful, purulent, destructive, extra-genital (extra-genital sites include the mouth and lips).[10,11,] It may also cause the syphilitic balanitis of Follman.[12, 13] An ano-genital ulcer should be considered as being caused by syphilis unless proven otherwise.

Secondary syphilis : multisystem involvement due to bacteraemia, which may recur up into the second year after infection - generalised non-itchy polymorphic rash often affecting the palms and soles, condylomata lata, mucocutaneous lesions, generalised lymphadenopathy; less commonly, patchy alopecia, uveitis [14, 15] otitis [16,,17] meningitis, cranial nerve palsies, hepatitis,[18] splenomegaly, periostitis and glomerulonephritis. The rash may be itchy, particularly in dark-skinned patients.[19] Uveitis, otitis, meningitis (i.e. early neurosyphilis) and other non-mucocutaneous symptoms may be the only symptom of early syphilis. [20,21]

Latent syphilis, early and late: positive serological tests for syphilis with no clinical evidence of treponemal infection. This is classified (ECDC definition) as early latent if the infection was acquired <1 year previously and as late latent if the infection was acquired >1 year previously[1]. Amplified definition of early latent syphilis: individuals who have had negative syphilis serology within one year of a syphilis diagnosis and who have no symptoms or signs of HIV disease, or individuals with positive syphilis serology who have unequivocal evidence that they have acquired syphilis in the previous twelve months.

Late Syphilis:
- Gummatous syphilis:[22] typical nodules/plaques or ulcers
- Neurosyphilis: ocular; auricular; meningovascular; parenchymatous (general paresis; tabes dorsalis); asymptomatic (abnormal CSF);
- Cardiovascular syphilis: aortitis - asymptomatic, angina, aortic regurgitation, stenosis of coronary ostia, aortic aneurysm (mainly thoracic)

Epidemiologic monitoring of infectious syphilis: all patients with primary, secondary and early latent syphilis should be reported to their national syphilis surveillance system and these national programmes should report to the European Surveillance of STI (ESSTI) network of the ECDC, if they are within the EU.[1]

B. Laboratory [4]

Demonstration of *Treponema pallidum* from lesions or infected lymph nodes in early syphilis:
- Darkfield microscopy[23]
- Polymerase chain reaction (PCR) [24, 25] – preferred method for oral and other lesions where contamination with commensal treponemes is likely. Occasionally PCR may also be a useful adjunct in the diagnosis of later stages, especially tertiary syphilis,[26] and also in congenital syphilis [27]
- A direct fluorescent monoclonal antibody test may also be used. However, access to suitable reagents limits the use of this test.

Serological tests for syphilis: [28,29,30,31,32]
None of the serological tests for syphilis differentiate between venereal syphilis (caused by *Treponema pallidum* subspecies *pallidum*) and the other treponematoses - yaws (*T. pallidum* subspecies *pertenue*), endemic syphilis (*T. pallidum* subspecies *endemicum*) and pinta (*T. pallidum* subspecies *carateum*). 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.
- Non-treponemal antigen tests (also referred to as cardiolipin antigen, lipoidal, or reagin tests): Rapid Plasma Reagin test (RPR) and the VDRL carbon antigen test (VDRL) are the most widely used of these tests. There are variants of these original tests such as the nowadays rarely used VDRL microflocculation test.

- Treponemal antigen tests (these tests use antigen from Nichol's strain of *T. pallidum* subspecies *pallidum,* derived directly or produced as a bacterial recombinant antigen): *Treponema pallidum* haemagglutination test (TPHA) – sometimes referred to as the Micro-Haemagglutination Assay for *T. pallidum* (MHA-TP), *Treponema pallidum* particle agglutination test (TPPA), Fluorescent Treponemal antibody absorption test (FTA-abs. test), Treponemal Enzyme immunoassay (EIA) – most of these tests now use recombinant antigen and detect total anti-treponemal antibody (IgG and IgM). The newer chemiluminescene immunoassays are likely to have the same role as screening tests as the current EIA tests.[33, 34].
- Specific anti-*Treponema pallidum* IgM antibody tests: 19S-IgM-FTA-abs test, IgM-immunoblot for *Treponema pallidum*, specific anti-*Treponema pallidum* IgM EIA.

Primary screening test:[30,31,32,35]

- A treponemal antigen test EIA or TPPA (preferred to TPHA) is recommended as a single screening test.
- Request a specific anti-treponemal IgM test if primary syphilis is suspected and/or perform a repeat test 1-2 weeks later.[36]
- Rapid treponemal tests might be useful in some circumstances provided positive results are confirmed serologically.[4]
- The RPR/VDRL is not recommended as a primary screening test.[4,36,37,38] It may be used for the rapid detection of symptomatic early syphilis in at-risk patients (supplemented with a standard recommended screening test). In these circumstances diluted as well as undiluted serum should be tested to prevent a false-negative test due to the prozone phenomenon.

Confirmatory test if any primary screening test is positive:[30,31,32,35]

- A treponemal antigen test of a different type from the primary screening test is recommended: TPPA (TPHA) if EIA is used for screening, EIA if TPPA (TPHA) is used for screening. If positive, the TPPA (TPHA) may be quantified if preferred.
- The IgG immunoblot using recombinant antigen is recommended as a supplementary confirmatory test, when a positive EIA screening test is not confirmed by the TPPA (TPHA) test or a positive TPPA (TPHA) screening test is not confirmed by the EIA test.[4,30,31,32,39]

The FTA-abs is not recommended as a standard confirmatory test.[40] However it could be used as a supplementary test in certain circumstances, e.g. in highly specialised laboratories with a large volume of confirmatory testing, where the quality of reagents and reproducibility of the test can be assured.

- Always repeat positive tests on a second blood specimen to confirm the results.

Tests for serological activity of syphilis:

- A quantitative RPR/VDRL is recommended when the confirmatory test is positive.

A titre of ≥ 32 is rarely seen after adequate treatment.[39] A titre of <32 or a negative VDRL/RPR test does not exclude active infection although active treponemal disease with a negative RPR/VDRL is unusual, more so in early syphilis than in late syphilis. A specific anti-treponemal IgM EIA is recommended when the confirmatory test is positive and an RPR/VDRL is negative in a patient with clinical signs suggestive of syphilis. In this situation a positive anti-treponemal IgM test indicates active infection.

A negative anti-treponemal IgM test does not exclude active infection, particularly in late infection.

Tests for monitoring the effect of treatment:

- A quantitative RPR/VDRL test is recommended for monitoring the serological response to treatment. The titre determined on a blood specimen taken on the day of treatment gives the baseline for measuring a decrease in titre.
- A specific anti-treponemal IgM EIA may be helpful in monitoring the serological response to treatment in RPR/VDRL negative primary syphilis.

B1. Laboratory: false negative syphilis serology[28,29]

- False negative treponemal screening tests may occur during the two to four week window period between acquiring infection and production of sufficient antibody (IgM and/or IgG) to result in a positive test.
- A false negative RPR/VDRL test may occur in secondary syphilis and early latent and early neurosyphilis due to the prozone phenomenon from using undiluted serum.
- False negative RPR/VDRL tests may occur in late-stage syphilis,[39] probably due to a gradual reduction of cardiolipin antibody over time. Sensitivity declines to 60-75%.
- Temporary negative serological tests (reactive on subsequent testing) have occasionally been reported in secondary syphilis.

B2. Laboratory: false positive syphilis serology[28,29]

- Occasional false positive reactions may occur with any of the serological tests for syphilis.
- In general, false positive reactions are more likely to be seen in autoimmune disease, HIV infection, pregnancy, and intravenous drug abuse.
- The FTA-abs test is particularly prone to false positive reactions in patients with autoimmune disease.
- The classical Biological False Positive (BFP) reaction (an antibody response to cardiolipin that is not due to syphilis) is much less of a problem now that treponemal antigen tests are recommended for screening. Traditionally BFP reactions were classified as acute (< 6 months) and chronic (>6 months). Acute BFP may be seen in pregnancy, post immunisation, recent myocardial infarction and in many febrile infective illnesses. Chronic BFP may be seen in injecting drug users, autoimmune diseases, leprosy, chronic liver pathology (chronic hepatitis B, chronic hepatitis C etc.) and old age.
- In the absence of a known history of syphilis or a positive anti-treponemal IgM test, persistent or transient reactivity in a single treponemal antigen test should be considered as a false positive serological test result.

C. Laboratory tests to confirm or exclude neurosyphilis[8,40,41]

- Lumbar puncture for examination of cerebrospinal fluid (CSF) is indicated in patients with positive syphilis serology and:[8,42]
    - clinical neurologic symptoms possibly caused by neurosyphilis

- clinical ocular symptoms possibly caused by ocular syphilis*
- clinical auricular (otologic) symptoms possibly caused by syphilitic otitis*
- concomitant HIV infection especially if CD4 count is <350/μl and / or the serum RPR test titre >1:32.** [7,35,43,44,45]

* Not obligatory in the absence of (other) clinical neurologic symptoms, provided treatment for neurosyphilis such as intravenous penicillin is given.[14,16]

** Not obligatory, but may be indicated in syphilis of unknown duration or in treatment failure. [44]

Criteria for the diagnosis of neurosyphilis in CSF [8,40,41,46]

TPHA/TPPA/MHA-P and /or FTA abs. test positive
and
Increased number of mononuclear cells (> 5-10/mm^3)
or
Positive VDRL/RPR

- No single test or clinical feature can diagnose neurosyphilis and a diagnosis is usually made on a combination of clinical presentation and the laboratory tests outlined above.
- Other considerations:
  - The number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (tabes dorsalis, general paresis).[31,32]
  - The VDRL test in CSF can be negative in neurosyphilis.[40,41,47,48]
  - A positive TPHA/MHA-TP/TPPA or FTA-absorption test in CSF by itself does not confirm the diagnosis neurosyphilis, but a negative treponemal CSF test excludes neurosyphilis.[41]
  - The criteria outlined above have not generally been validated in HIV sero-positive patients.
  - A TPHA index as defined by Luger and Schmidt in 2000 (TPHA-index Vienna 2000) is used by some specialists as a laboratory criterion to diagnose neurosyphilis and has been noted to have a higher sensitivity than the CSF-VDRL test. [8,41]
  - The TPHA index Vienna 2000 (CSF TPHA/albumin quotient [CSF albumin x 10^3/serum albumin]) takes into account impairment of the blood-brain barrier and is more sensitive than the CSF VDRL test whilst maintaining high specificity.[21,23]
  - A TPHA index Vienna 2000 of >70 and a CSF TPHA titre >320 are the most reliable in supporting a diagnosis of neurosyphilis. [8,41]
  - Neurosyphilis is unlikely when the CSF TPHA titre is < 320

D. Screening test to exclude asymptomatic cardiovascular syphilis

- Chest radiograph

E. Investigation for ocular syphilis

Any patient with unexplained sudden visual loss should be screened for syphilis. Uveitis may be the only symptom of early syphilis and can be cured without permanent visual loss if treated adequately without delay. 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 [42,44,49,50,51,52, 53, 54,55]

Individuals with syphilis are at higher risk of acquiring other infectious diseases. All individual syphilis patients should be tested for HIV and HCV and evaluated for hepatitis B and if necessary vaccinated. All individuals with syphilis should have a full STI assessment.

General remarks[5,53]

- A treponemocidal level of antimicrobials 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 treponemocidal, but is substantially lower than the maximally effective in vitro level of concentration, which is far higher (0.36 mg/l).[49,53,56]
- Duration of treponemocidal 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 Longer duration of treatment is needed as the duration of infection increases (more relapses were seen in later stages after short courses of treatment), possibly because of more slowly dividing treponemes in late syphilis. Treponemes have been shown to persist despite apparently successful treatment.[50] The significance of this finding, if any, is unknown.
- Long acting Benzathine penicillin 2.4 million units provides a treponemocidal penicillinaemia for up to 3-4 weeks (21-23 days).[56, 57] 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.
- The recommendations for late syphilis are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinion, case studies and past clinical experience.[49]
- Parenteral rather than oral penicillin treatment has generally been the treatment of choice because parenteral therapy is supervised with guaranteed bioavailability. Oral fenoxymethylpenicilline is a possible option, though there is more evidence for the use of amoxicillin in this situation.[58] Amoxicillin given orally in combination with probenecid appears to be effective and results in treponemocidal CSF levels.[59,60]
- Non-penicillin antibiotics that have been evaluated are tetracyclines, including doxycycline, which is the preferred tetracycline with penetration into the CSF [49,50, 61,62] and erythromycin, all taken orally. Erythromycin is least effective and does not penetrate the blood-brain or placental barriers well.[50] Newer antitreponemals include intramuscular or intravenous ceftriaxone.[5,35,53,63,64,] Ceftriaxone has good CSF penetration, however it requires multiple injections and offers few advantages to single dose Benzathine penicillin.[7,65] Like oral doxycycline daily

intramuscular ceftriaxone may be an alternative for early syphilis patients with penicillin allergy, although penicillin anaphylaxis is considered an absolute contraindication.[7,35,53,66]

- Azithromycin shows good anti-treponemocidal activity in animal studies and early open studies showed it appears effective in early syphilis.[49,67,68,69] These findings have been confirmed by a recent randomised controlled study.[70] However, intrinsic resistance to azithromycin has been described in some *T.pallidum* strains [35,71,72,73]
- The host immune response is important as 60% of untreated patients go through life without developing late complications.[74] CSF involvement is common in early syphilis.[75,76] Although both parenteral Benzathine penicillin and standard regimens of parenteral procaine penicillin do not achieve treponemocidal CSF levels,[42,49,77,78] the prevalence of late syphilis, including neurosyphilis, remains low,[46] indicating that treatment is effective and suggesting that host immune responses in early syphilis play an essential part.
- Benzathine penicillin is widely used because of efficacy and ease of treatment. Replacing half of the solvent by lidocaine 1% solution may reduce the pain associated with injection[79] and may improve compliance. Compliance with daily intramuscular injections with procaine penicillin has been good in the UK.[80] The control of syphilis over the past 50 years has been excellent 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 adequate, although there remains a need for properly controlled studies.
- HIV co-infection with syphilis does not appear to increase the risk of developing a more aggressive course with (early) neurosyphilis, treatment failure or relapse. [7,10,11,44,81] In early syphilis HIV-infection may be a risk factor for symptomatic early neurosyphilis (ocular and auricular syphilis and meningitis). [21,82] Therefore an HIV antibody test should always be recommended for all patients with syphilis. [62,83,84] HAART also appears to decrease the risk of early neurosyphilis in HIV-positive patients.[21] Some specialists recommend routine CSF- examination in HIV-positive patients with late latent syphilis or latent syphilis of unknown duration to exclude asymptomatic neurosyphilis.

<u>Recommended regimens</u>

<u>Early syphilis (primary, secondary and early latent)</u> [2,42,44,49,51,52,53,54,85,86]

First line therapy options:

- Benzathine penicillin 2.4 million units IM (each buttock 1.2 million units- although some specialists recommend 2.4 units as a single injection) on day 1.[2,42,44,49,51,52,53,54,70,] (Ib A)
  Replacing half of the solvent by lidocaine 1% solution may reduce the discomfort associated with the injection.

- Procaine penicillin 600,000 units IM daily for 10-14 days.[2,51,52,56,73] (IIb B)

Penicillin allergy or parenteral treatment refused:

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) oral for 14 days.[2,49,50,61,62] (III B)
- Tetracycline 500 mg orally four times oral daily for 14 days.[2,49,50] (IIIB)
- Erythromycin 500 mg four times oral daily for 14 days.[49,50] (IV C)
- Azithromycin 2 gm oral as a single dose.[70] (IB) (see text for details of recommendation)

Note: Ceftriaxone 500 mg i.m. daily for 10 days is an option if parenteral treatment is not refused however there is significant cross reaction between cephalosporins and penicillin and anaphylaxis for penicillin is an absolute contraindication to the use of Ceftriaxone.[35,53](IB)

Late latent syphilis, cardiovascular and gummatous syphilis

First line therapy options:

- Benzathine penicillin 2.4 million units IM (each buttock 1.2 million units or 2.4 million units as a single dose) weekly on day 1, 8 and 15.[2,44,49,52,53,54] (III B) Replacing half of the solvent by lidocaine 1% solution may reduce the discomfort associated with the injection.
- Procaine penicillin 600,000 units IM daily for 17 – 21 days.[52,53,54,87,73] (III B)

Penicillin allergy or parenteral treatment refused:

Some specialists recommend penicillin desensitisation as the evidence base for the use of non-penicillin regimes is relatively weak.[7,44]

Alternative regimes include:

- Doxycycline 200 mg daily (either as 100 mg twice daily or a single 200 mg dose) for 21-28 days.[2,44,49,52] (IV C)
- Tetracycline 500 mg four times daily for 28 days.[2] (IV C)
- Erythromycin 500 mg four times daily for 28 days.[49] (IV C)

Symptomatic neurosyphilis (including ocular and auricular syphilis) and asymptomatic neurosyphilis

- Biological plausibility suggests that regimens that achieve treponemocidal levels of an antibiotic in the CSF should be the treatment of choice. Options are intravenous (IV) or intramuscular(IM)/ combined with oral probenecid. Data comparing these two options are lacking.
- There are conflicting data over the effectiveness of producing treponemocidal CSF penicillin level using the procaine penicillin/probenecid combination.[50,87,88,89]. Concern raised, that the CSF penicillin is increased at the expense of CNS tissue level, may not be relevant, because the levels in both CSF and CNS tissue are in fact higher with probenecid than without, with a significantly higher level in the CSF.[47] The experience in the UK with treatment of neurosyphilis with the procaine penicillin/probenecid combination has been positive so far. However the availability of probenecid may be a problem.
- In ocular syphilis (which can occur as a form of early neurosyphilis, a complication of early syphilis, but can also occur in late syphilis), especially in uveitis syphilitica of short duration, effective treatment can be achieved with parenteral Benzathine penicillin,[90,91] but generally intravenous therapy is preferred. Some studies suggest that patients with serious ocular involvement or ocular involvement of longer duration (with threat of permanent loss of vision) or ocular syphilis plus other signs of symptomatic (early) neurosyphilis (e.g. auricular syphilis or meningitis), should be treated with intravenous penicillin.

- CSF abnormalities are slower to normalize in HIV patients, particularly if the peripheral blood CD4 lymphocyte count is<200/μl.[93]

First line therapy:
- Benzyl penicillin 12-24 million units IV daily, as 3-4 million units every 4 hours during 18-21 days.[2,44,49,51,52,53,54] (III B)
- Benzyl penicillin 0.15 million units/kg/day IV, spread over 6 doses (every 4 hours) for 10-14 days.[89] (III B)
- Procaine penicillin 1.2-2.4 million units IM daily PLUS Probenecid 500 mg four times daily, both during 10-17 days.[2,50,52] (IIb B)

Penicillin allergy or parenteral treatment refused:
- Doxycycline 200mg twice per day for 28 days.[52,61] (IV C)

Note: The evidence for the use of non-penicillin regimes in the treatment of neurosyphilis is relatively weak and some specialists recommend desensitisation for all patients with neurosyphilis who have penicillin allergy.[7,44,52]

Follow-up: repeat CSF examination should be undertaken 6-12 months after treatment of symptomatic neurosyphilis.[21, 93]

Special situations

Pregnancy

First line options for treatment of early syphilis (acquired <1 year previously):

- Benzathine penicillin 2.4 million units IM as a single dose (1.2 million units in each buttock or 2.4 million units as a single dose.[9,94,95] (I B)

Note: Some specialists recommend two doses of Benzathine penicillin 2.4 million units (Day 1 and day 8) for pregnant women with early syphilis because of altered pharmacokinetics during pregnancy (shortened drug half life) particularly in the last trimester. [9,52] (III B)

- Procaine penicillin 600,000 - 1.2 million units IM daily during 10 – 14 days. [52,80] (III B)

Penicillin allergy:

- Desensitisation to penicillin should be considered followed by first line treatment.[2,44,52,96]
  - Erythromycin 500 mg qds for 14 days (evidence level IV C). As treatment failure has been recognised with this regime consideration should be given to re-treating mothers with doxycycline after delivery.
  - Ceftriaxone 500 mg IM for 10 days. There is a significant risk of cross hypersensitivity with this agent and penicillin and patients with previous penicillin anaphylaxis should not receive Ceftriaxone.

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

- Recommendation: all pregnant women should be screened at first antenatal appointment for syphilis. Whether or not this should be repeated subsequently in pregnancy depends on the local epidemiology of syphilis within the population being screened. A number of different approaches to screening intervals have been adopted in other countries, and those of the USA and the Russian Federation are cited below.

- Serological screening is recommended in the USA at: a) initial antenatal appointment; b) 28 weeks of gestation; c) delivery, if high risk for congenital syphilis[44]. In The Russian Federation it is recommended at: a) initial antenatal appointment; b) 21 weeks of gestation; c) 36 weeks of gestation.[3]

- Each country should decide on its own screening policy, if possible based on a cost-effectiveness analysis.

- Although some specialists recommend that 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,[2,44] there is evidence which suggests that this is probably not necessary.[94,95] -This is probably especially true if treatment of the mother occurs before 28 weeks gestation. [9]

- The treatment of late syphilis in pregnancy. Women with late syphilis who are pregnant can be treated with penicillin based regimes as for non-pregnant individuals (see above).

Congenital syphilis

A. Diagnosis

Confirmed congenital infection:
T. pallidum demonstrated by dark field microscopy or PCR , in placenta or autopsy material, exudates from suspicious lesions, or body fluids, e.g. nasal discharge .

Presumed congenital infection:[2,9,44,51,97].

- 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 RPR/VDRL test in the cerebrospinal fluid;
  - a fourfold increase or more of the TPPA(TPHA) titre in the child's as opposed to the mother's serum (both obtained simultaneously at birth);
  - a fourfold increase or more of the titre of a non-treponemal test in the child's as opposed to the mother's serum (both obtained simultaneously at birth);
  - a fourfold increase or more of the titre of a non-treponemal or treponemal test within 3 months after birth;
  - a positive anti-treponemal IgM EIA, 19S-IgM-FTA-abs test 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.
- In a child >12 months of age with a positive treponemal serologic test for syphilis.

Late congenital syphilis including clinical presentation:

- Interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddle nose 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.
- All patients with congenital syphilis should be reported to the national syphilis surveillance system.

B. Investigations

- RPR/VDRL, TPPA (TPHA) (quantitative), anti-treponemal IgM EIA, treponemal IgM (19S-IgM FTA-abs test or IgM-immunoblot) – from infant's blood and not umbilical cord blood, because false-positive and -negative tests may result.
- Blood: Full blood count, liver function, electrolytes
- CSF : cells, protein, RPR/VDRL, TPHA/TPPA
- X-rays long bones
- Ophthalmic assessment as indicated

C. Treatment options

- Benzyl penicillin 150,000 units/kg IV daily (administered in 6 doses every 4 hours) during 10-14 days (IV C)
- Procaine penicillin 50,000 units/kg IM daily x 10-14 days (IV C)

- If CSF is normal: Benzathine penicillin 50,000 units/ kg IM (single dose) (IV C)

HIV infected patients[44]

A. 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.
- Patients with HIV co-infection may have a slower rate of decline of VDRL/RPR after treatment and this should not be considered failure of response to treatment.
- False negative and positive tests and delayed appearance of seroreactivity have been reported.[42,49]
- In HIV infected individuals with clinical suspicion of syphilis and a negative treponemal screening test, it is advisable to perform supplementary treponemal tests and if these are also repeatedly negative then other diagnostic tests e.g. PCR, histological or immunofluorescent examination of a biopsy from a clinically suspected lesion and direct darkfield microscopy or PCR of the exudates of early syphilitic lesions for spirochaetes.
- The evidence that HIV infected patients with early syphilis may have an increased risk of (early) asymptomatic neurological involvement and higher rate of treatment failure with Benzathine penicillin compared to non-HIV-infected patients was confined to case reports, [42,49,52] but recent evidence suggests that that risk may be increased, although the evidence is still not conclusive careful follow-up is essential. [43,93]
- Some specialists recommend CSF examination as part of the assessment of HIV-infected patients with late latent syphilis or latent syphilis of unknown duration (see “General remarks” in “Management”).

B. Treatment of syphilis in patients with concomitant HIV-infection

- Treatment should be given as for non-HIV-infected patients.
  Note: Careful follow-up is essential (see above).

Reactions to treatment

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

A. 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 foetal 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 prevent the febrile episode.[98] Although steroids are unproven at ameliorating local infection, as there can be severe deterioration in early syphilis with optic neuritis and uveitis, steroids should be used as biological plausibility would suggest that it is likely to be useful (see below).
- Systemic treatment with a blocker of Tumour-Necrosis-Factor (TNF) may be more effective than systemic treatment with a corticosteroid[99].

- Management
  - If cardiovascular or neurological involvement (including optic neuritis) exists, inpatient management is advisable.
  - Prevention of Jarisch-Herxheimer reaction, prednisolone 20-60mg daily for 3 days, starting anti-treponemal treatment after 24 hours of commencing prednisolone.[98] (IV C)
  - Antipyretics

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

- Due to inadvertent intravenous injection of procaine penicillin and may be minimised by the "aspiration technique" of injection.
- Characterised 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 5-10mg rectally / IV / IM if convulsions

C. Anaphylactic shock

- Facilities for treatment of anaphylaxis should be available as penicillin is one of the commonest causes.

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

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 and confirmation of any past treatment history.
- Clear information ideally in writing should be given to all individuals with syphilis and their sexual contacts.
- 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) may be due to probable early, infectious, latent syphilis[42].

- Partner notification assists community efforts to reduce the disease burden, helps to identify asymptomatic patients with syphilis and can delineate the sexual risk networks hosting transmission. Partner notification programs in outbreaks associated with a high rate of untraceable partners need to adopt innovative approaches to partner notification, including use of the internet and community outreach programs.[42]
- Sexual partners should include all those individuals who have had oral, vaginal or anal intercourse with infected individuals, whether or not barrier protection was used.
- 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, 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 clinical and serological response to treatment.[6]

- Early syphilis, minimum clinical and serological assessment (VDRL/RPR): 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 and 24 months[44,51]
  - After treatment of early syphilis the titre of non-treponemal tests (e.g. VDRL and/or RPR) should decline by 2 dilution steps (4 fold) within 6 months (within 12 months for HIV-positive patients).[6] However, about 15% or more of primary and secondary syphilis HIV-negative patients do not have a fourfold decrease of the RPR test titre at 6 months, the significance of which (in asymptomatic patients) is unknown.[85,100]
  - If a four-fold decline of the titre of a non-treponemal test this does not occur after 6-12 months, some experts recommend additional treatment (according to the CDC[27]: Benzathine penicillin 2.4 million units IM on days 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 non-treponemal tests is often absent. In non-HIV-infected late latent syphilis patients with a reactive non-treponemal test, which remains stable after adequate therapy (serofast between two tests taken three months apart), follow-up after treatment is generally not indicated.[6]

- An increase of ≥ 2 dilution steps (4 fold) in a non-treponemal test confirmed on a second specimen suggests reinfection or reactivation.[6]
- Follow-up examination of cerebrospinal fluid 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 retreatment.
- Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.

The guideline group conducted a literature review which included searching Medline for the years 1990 to 2008 and using the keywords "syphilis" and "syphilis and HIV" plus additional MeSH headings "neurosyphilis", "cardiovascular syphilis", "latent syphilis" and "syphilis and

treatment". Only English language papers were searched. The guideline revision was also based on the conclusions of a IUSTI /WHO workshop of 2004 (see references 4,5,6,7,8,9). A review of older references were identified by examining key overviews of syphilis (see references 42,49,54,55,101) and a review of syphilis treatment that specifically focused on syphilis management in Europe (reference 53)

References

1. European Union. European Centre for Disease Prevention and Control. http://ecdc.europe.eu and www.essti.org

2. World Health Organisation. Sexually Transmitted Infections Management Guidelines 2004. http://www.who.int/HIV_AIDS

3. Goh B, Van Voorst Vader PC. European Guideline for the management of syphilis. Int J STD AIDS 2001; 12 (Suppl 3): 14-26. www.iusti.org

4. Young H, Van Voorst Vader PC. Standard serologic testing for syphilis in individual patients: the European view. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

5. Parkes R, Van Voorst Vader PC. Treatment of syphilis in Europe. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

6. French P, Van Voorst Vader PC. Serologic follow-up after treatment for syphilis in Europe. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

7. Janier M, Van Voorst Vader PC. Syphilis and HIV infection: the European view. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

8. Schmidt BL, Van Voorst Vader PC. Laboratory diagnosis of neurosyphilis in Europe. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

9. Mabey D, Van Voorst Vader PC. Prevention of congenital syphilis in Europe. IUSTI/WHO Conference on STI. Europe Syphilis Guideline Expert Workshop. Mykonos, Greece, 2004.

10. Rompalo AM, Joesoef MR, O'Donnell JA, Augenbraun M, Brady W, Radolf JD, et al. Clinical manifestations of early syphilis by HIV status and gender. Results of the Syphilis and HIV study. Sex Transm Dis 1997; 28: 158-65.

11. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. Sex Transm Dis 2001; 28: 448-54.

12. Eccleston K, Collins L, Higgins SP. Primary syphilis. Int J STD & AIDS 2008; 19: 145-51.

13. Leiman K,Starzycki Z. Syphilitic balanitis of Follman developing after the appearance of the primary chancre. Brit J Ven Dis 1975; 51: 138-40.

14. Browning DJ. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy and the influence of human immunodeficiency virus status on response. Ophthalmology 2000; 107: 2015-23.

15. Parc CE, Chahed S, Patel SV, Salmon-Ceron D. Manifestations and treatment of ocular syphilis during an epidemic in France. Sex Transm Dis 2007; 34: 553-6.

16. Mishra S, Walmsley SL, Loutfy MR, Kaul R, Logue KJ, Gold WL. Otosyphilis in HIV-coinfected individuals: a case series from Toronto, Canada. AIDS Patient Care and STDs 2008; 22: 213-9.

17. Jeans AR, Wilkins EGL, Bonington A. Sensorineural hearing loss due to secondary syphilis. Int J STD AIDS 2008; 19: 355-6.

18. Noto P, Del Nonno F, Licci S, Chinello P, Petrosillo N. Early syphilis hepatitis in an immunocompetent patient: really so uncommon? Int J STD AIDS 2008; 19:56-6.

19. Chapel TA. The signs and symptoms of secondary syphilis. Sex Transm Dis 1980; 7: 151-4.

20. Lee MA, Aynalem G, Kerndt P, Tabidze I, Gunn RA,Olea L, et al. Symptomatic early neurosyphilis among HIV-positive men who have sex with men – four cities, United States, January 2002 – June 2004. MMWR 2007; 56: 625-8.

21. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS 2008; 22: 1145-51.

22. Weinert LS, Scheffel RS, Zoratto G, Samios V, Jeffmann MW, Dora JM, et al. Cerebral syphilitic gumma in HIV-infected patients: case report and review. INt J STD AIDS 2008; 19: 62-4.

23. Wheeler HL, Agarwal S, Goh BT. Dark Ground microscopy and treponemal serological tests in the diagnosis of early syphilis. Sex Transm Infect 2004; 80: 411-4.

24. Palmer HM, Higgins SP, Herring AJ, Kingston MA. Use of PCR in the diagnosis of early syphilis in the United Kingdom. Sex Transm Infect 2003; 79: 479-83.

25. Koek AG, Bruisten SM, Dierdorp M, Van Dam AP, Templeton K. Specific and sensitive diagnosis of syphilis using a real-time PCR for *Treponema pallidum*. Clin Microbiol Infect 2006; 12: 1233-6.

26. Zoechling N, Schluepen EM, Soyer HP, Kerl H, Volkenandt M. Molecular detection of *Treponema pallidum* in secondary and tertiary syphilis. Br J Dermatol 1997; 136: 683-686.

27. Salojee H, Velaphi S, Goga Y, Afadapa N, Steen R, Lincetto O. The prevention and management of congenital syphilis: an overview and recommendation. Bull World Health Organ 2004; 82: 424-30.

28. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev 1995; 8: 1-21.

29. Nandwani R, Evans DTP. Are you sure it's syphilis? A review of false positive serology. Int J STD & AIDS 1995; 6: 241-8.

30. Egglestone SI, Turner AJL. Serological diagnosis of syphilis. Commun Dis Public Health 2000; 3: 158-62.

31. Young H. Guidelines for serological testing for syphilis. Sex Transm Inf 2000; 76: 403-5.

32. Lewis DA, Young H. Testing guidelines for individual sexually transmitted infections - Syphilis. In: Ross J, Ison C (eds). UK national screening and testing guidelines for sexually transmitted infections. Sex Transm Infect 2006; 82, Suppl 4: iv13 - iv15.

33. Marangoni A, Vittorios, Accardo S, Cavrini F, D'Antuono A, Moroni A, et al. Evaluation of LIASON Treponema Screen, a novel recombinant antigen-based Chemiluminesceneimmunoassay for laboratoray diagnosis of syphilis. Clin Diagn Lab Immunol 2005; 12: 1231-4.

34. Hagedorn HJ, Kraminer-Hagedorn A, De Bosschere K, Hulstaert F, Pottel H, Zrein M. Evaluation of INNO-LIA syphilis assay as a confirmatory test for syphilis. J Clin Microbiol 2002; 40: 973-8.

35. Stoner BP. Current controversies in the management of adult syphilis. Clin Infect Dis 2007; 44 (Suppl 3): S130-46.

36. Manavi K, Young H, McMillan A. The sensitivity of syphilis assays in detecting different stages of early syphilis. Int J STD AIDS 2006; 17: 768-71.

37. Geusau A, Kittler H, Hein U, Dangl-Erlach E, Stingl G, Tschachler E. Biological false-positive tests comprise a high proportion of Venereal Disease Research Laboratory reactions in an analysis of 300,000 sera. Int J STD AIDS 2005; 16: 722-6.

38. Creegan L, Bauer HM, Samuel MC, Klausner J, Liska S, Bolan G. An evaluation of the relative sensitivities of the Venereal Disease Research Laboratory test and the *Treponema pallidum* Particle Agglutination test among patients with

primary syphilis. Sex Transm Dis 2007; 34: 1016-8.

39. Luger AFH. Serological diagnosis of syphilis: current methods. In: Young H, McMillan A. (eds). Immunological diagnosis of sexually transmitted diseases. New York: Marcel Dekker, 1988; pp 249-74.

40. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. JAMA 1972; 219: 726-9.

41. Luger AF, Schmidt BL, Kaulich M. Significance of laboratory findings for the diagnosis of neurosyphilis. Int J STD & AIDS 2000; 11: 224-34.

42. Van Voorst Vader PC. Syphilis management and treatment. Dermatol Clin 1998; 16: 699-711.

43. Marra C, Maxwell CL , Smith SL , Lukehart SA , Rompalo AM, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 2004; 189: 369-76.

44. Centers for disease control and prevention. Sexually transmitted diseases treatment guidelines 2006. MMWR 2006; 55: No RR-11 and www.cdc.gov/std

45. Libois A, De Wit S, Poll B, Garcia F, Florence E, DelRio A, et al. HIV and syphilis: when to perform a lumbar puncture. Sex Transm Dis 2007; 34: 141-4.

46. Perdrup A, Jorgensen BB, Stranberg Pedersen N. The profile of neurosyphilis in Denmark. A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971-1979. Acta Dermatovener (Stockh) 1981; Suppl 96: 3-14.

47. Van Eijk RVW, Wolters EC, Tutuarima JA, Hische EAH, Bos JD, Van Trotsenburg L, et al. Effect of early and late syphilis on central nervous system: cerebrospinal fluid changes and neurological deficit. Genitourin Med 1987; 63: 77-82.

48. Wolters EC, Hische EAH, Tutuarima JA, Van Trotsenburg L, Van Eijk RVW, Bos JD, et al. Central nervous system involvement in early and late syphilis: the problem of asymptomatic neurosyphilis. J Neurol Sciences 1988; 88: 229-39.

49. Rolfs RT. Treatment of Syphilis, 1993. Clin Infect Dis 1995; 20 (Suppl1): S23-38.

50. Dunlop EMC. Survival of treponemes after treatment, comments, clinical conclusions and recommendations. Genitourin Med 1985; 61: 293-301.

51. Brockmeyer NH. Syphilis. In: Petzoldt D, Gross G (eds). Diagnostik und Therapie sexuell übertragbarer Krankheiten. Berlin, Springer Verlag, 2001: 101-11

52. BASHH Clinical Effectiveness Group. UK National Guidelines on Early and Late Syphilis 2008. www.BASSH.org.uk

53. Parkes R, Renton A, Meheus A, Laukamm-Josten U. Review of current evidence and comparison for effective syphilis treatment in Europe. Int J STD & AIDS 2004; 15: 73-88.

54. French P. Syphilis. BMJ 2007; 334: 143-7

55. Goh BT. Syphilis in adults. Sex Trans Infect 2005; 81: 448-52.

56. Idsøe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis. The experience of three decades. Bull WHO 1972; 47: 1-68.

57. Akovbyan VA, Kubanova AA, Toporovsky LM, Akovbyan GV, Fedoriova LD, Sorkin RZ, et al. Benzylpenicillin benzatine (Extencillin) in the treatment of syphilis: five-year experience. Vestnik Dermatologii iVenerologii 1998; nr 4: 61-4 (Russian language).

58. Löwhagen GB, Johannison G, Roupe. Alternative treatment of early syphilis – comparison between oral penicillin V and intramuscular procaine penicillin. Eur J Sex Transm Dis 1984; 1: 159-64.

59. Faber WR, Bos JD, Tietra PJGM, Fass H, Van Eijk RVW. Treponemicidal levels of amoxycilin in cerebrospinal fluid after oral administration. Sex Transm Dis 1983; 10: 148-50.

60. Morrison RE, Harrison SM, Tramont EC. Oral amoxycillin, an alternative treatment for neurosyphilis. Genitourin Med 1985; 61: 359-62.

61. Whiteside Yim C, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. Antimicrobial Agents Chemother 1985; 28: 347-8.

62. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. CID 2006; 42:e45-e49.

63. Marra CM, Boutin P, McArthur JC, Hurwitz S, Simpson PA, Haslett JA, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis 2000; 30: 540-4.

64. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. Am J Med 1992; 93: 481-8.

65. Smith NH , Musher DM , Huang DB, Rodriguez PS, Dowell ME, Ace W, et al. Response of HIV infected patients with asymptomatic syphilis to intensive

intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD & AIDS 2004; 15: 328-32.

66. Augenbraun MH. Treatment of syphilis, 2001: nonpregnant adults. Clin Infect Dis 2002; 35: S187-90.

67. Verdon MS, Hunter Handsfield H, Johnson RB. Pilot study of azithromycin for treatment of primary and secondary syphilis. Clin Infect Dis 1994; 19: 486-8.

68. Mashkilleyson AL, Gomberg MA, Mashkilleyson N, Kutin SA. Treatment of syphilis with azithromycin. Int J STD & AIDS 1996; 7 (Suppl 1): 13-5.

69. Gruber GF, Kastelan M, Cabrijan L, Simonic E, Brajac I. Treatment of early syphilis with azithromycin. J Chemother 2000; 12: 240-3.

70. Riedner G, Rusizoka M, Todd J, Maboko L, Hoelscher M, Mmbando D, et al. Single-Dose Azithromycin versus Penicillin G Benzathine for the treatment of Early Syphilis. N Eng J Med. 2005; 353: 1236-44.

71. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin resistant syphilis infection: San Francisco, California, 2000-2004. Clin Infect Dis 2006; 42: 337-45.

72. Stamm LV, Stapleton JT, Bassford PJ. In vitro assay to demonstrate high-level erythromycin resistance of a clinical isolate of *Treponema pallidum*. Antimicrob Agents Chemother 1988; 32: 164-9.

73. Lukehart SA, Godornes C, Molini B, Sonnett P, Hopkins S, Mulcahy F, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. N Engl J Med 2004; 351: 154-8.

74. Gjestland T. An epidemiological investigation of the natural course of the syphilitic infection based upon a restudy of the Boeck-Bruusgaard material. Acta Derm Venereol (Stockh) 1955; 35: Suppl 34.

75. Löwhagen GB, Andersson M, Blomstrand C, Roupe G. Central nervous system involvement in early syphilis. Part I. Intrathecal immunoglobulin production. Acta Derm Venereol (Stockh) 1983; 63: 409-17.

76. Löwhagen GB, Rosenhall U, Andersson M, Blomstrand C, Lindholm L, Roupe G. Central nervous system involvement in early syphilis. Part II. Correlation between auditory brainstem responses and cerebrospinal fluid abnormalities. Acta Derm Venereol (Stockh) 1983; 63: 530-5.

77. Löwhagen GB, Brorson J-E, Kaijser B. Penicillin concentrations in cerebrospinal fluid and serum after intramuscular, intravenous and oral administration to syphilitic patients. Acta Derm Venereol (Stockh) 1983; 63: 53-7.

78. Goh BT, Smith GW, Samarasinghe L, Singh V, Lim KS. Penicillin concentrations in serum and cerebrospinal fluid after intramuscular injection of aqueous procaine penicillin 0.6 MU with and without oral probenecid. Br J Venereol Dis 1984; 60: 371-3.

79. Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J 1998; 17: 10. 890-893.

80. Crowe G, Theodore C, Forster GE, Goh BT. Acceptability and compliance with daily injections of procaine penicillin in the treatment of syphilis-treponemal infection. Sex Transm Dis 1997; 24: 127-30.

81. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without HIV infection. N Engl J Med 1997; 337: 307-14.

82. Lee MA, Aynalem G, Kerndt P et al. Symptomatic early syphilis among HIV-positive men who have sex with men. – Four cities. United States March 2002 – June 2004 MMWR 2007: 56(25); 625-8.

83. Manavi K, Macmillan A. The outcome of treatment on early latent syphilis and syphilis with undetermined duration in HIV-infected and HIV-uninfected patients. Int J STD AIDS 2007; 18: 814-8.

84. Ghanem KG, Erbelding EJ, Wiener ZS, Rompalo AM. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sex Trans Infect 2007; 83: 97-101.

85. Rolfs RT. Treatment of syphilis, 1993. Clin Inf Dis 1995; 20 (Suppl 1): S23-38.

86. Perdrup A. Penicillin treatment of early syphilis. A follow-up study of 213 patients observed for 1-11 years. Comparison between the effect of six and twelve million units. Acta Derm Venereol 1960; 40: 340-57.

87. Dunlop EMC, Al-Egaily SS, Houang ET. Penicillin concentrations in CSF during repository treatment for syphilis. Genitourin Med 1990; 66: 227-8.

88. Van der Valk PGM, Kraai EJ, Van Voorst Vader PC, Haaxma-Reiche H, Snijder JAM. Penicillin concentrations in cerebrospinal fluid (CSF) during repository treatment regimen for syphilis. Genitourin Med 1988; 64: 223-4.

89. Schoth PEM, Wolters EC. Penicillin concentrations in serum and CSF during high-dose intravenous treatment for neurosyphilis. Neurology 1987; 37: 1214-6.

90. Wilhelmus KR, Yokoyama CM. Syphilitic episcleritis and scleritis. Am J Ophthalmol 1987; 104: 595-7.

91. Ross WH, Sutton HFS. Acquired syphilitic uveitis. Arch Ophthalmol 1980; 98: 496-8.

92. Browning DJ. Posterior segment manifestations of active ocular syphilis their response to a neurosyphilis regimen of penicillin therapy and the influence of human immunodeficiency virus status on response. Ophthalmology 2000; 107: 2014-23.

93. Marra CM, Maxwell CL, Tantalo L, Eaton M, Rompalo AM, Raines C, et al. Normalization of CSF fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis 2004; 38: 1001-6.

94. Watson Jones D, Changalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, et al. Syphilis in Pregnancy in Tanzania I. Impact of Maternal Syphilis on Outcome of Pregnancy. J Infect Dis 2002: 186: 940-947.

95. Watson-Jones D, Gomodoka B, Weiss H, Changalucha J, Todd J, Mugeye K, et al. Syphilis in Pregnancy in Tanzania II. The effectiveness of Antenatal Screening and Single-dose Benzathine Penicillin Treatment for the Prevention of Adverse Pregnancy Outcomes. J Infect Dis 2002; 186: 948-57.

96. Wendel GO, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitisation in serious infections during prgnancy. N Eng J Med 1985 ; 312: 1229-32.

97. Boot JM, Oranje AP, De Groot R, Tan G, Stolz E. Congenital syphilis. Int J STD & AIDS 1992; 3: 161-7.

98. Gudjonsson H, Skog E. The effect of prednisolone on the Jarisch-Herxheimer reaction. Acta Dermatol Venereol 1968; 48: 15-18.

99. Fekade DF, Knox K, Hussein K, Melka A. Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor. New Engl J Med 1996; 335: 311-5.

100. Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. Ann Int Med 1991; 114: 1005-9.

101. Stoner BP. Current controversies in the management of adult syphilis. Clin Infect Dis 2007; 44 (Suppl 3): S130-46.

Appendix

The Syphilis Guideline Revision Group

Dr Patrick French (Chair)
Camden Primary Care Trust and Univerity College London
The Mortimer Market Centre
Mortimer Market
London WC1E 6JB
UK

Dr Mikhail Gomberg
Head of STD Division
Central Research Institute for Skin and Venereal Diseases
Korolenko 3
Moscow 107076
Russia

Dr Michel Janier
Centre Clinique des M.S.T.
Hopital Saint-Louis
1 Avenue Claude Vellefaux
75475 Paris
Cedex 10
France

Dr Bruno L. Schmidt
Serodiagnostiche Station
Krankenhaus der Stadt Wien – Hietzing
Mit Neurologischem Zentrum Rosenhugel
Wokersbergenstrasse 1
A1130 Wien
Austria

Dr Pieter C. van Voorst Vader
Department of Dermatology
University Medical Centre Groningen
PO Box 30.001
9700 RB Groningen
The Netherlands

Dr Hugh Young
The Scottish Bacterial Sexually Transmitted Reference Laboratory
Microbiology
Edinburgh Royal Infirmary
51 Little France Crescent
Edinburgh EH16 4SA
UK

Syphilis treatment: Treatment Summary with levels of evidence and grading of recommendations.

Stage of syphilis	Therapy	Level of evidence	Grading of recommendation
Early syphilis (primary, secondary and early latent)	Benzathine penicillin 2.4 million units IM	Ib	A
Early syphilis (primary, secondary and early latent)	Procaine penicillin 600,000 units IM	IIb	B
Early syphilis (primary, secondary and early latent)	Doxycycline 200 mg daily orally (either 100mg twice daily or a single 200mg dose)	III	B
Early syphilis (primary, secondary and early latent)	Tetracycline 500mg orally 4x daily for 14 days	III	B
Early syphilis (primary, secondary and early latent)	Erythromycin 500mg 4x daily orally for 14 days	IV	C
Early syphilis (primary, secondary and early latent)	Azithromycin 2g orally as a single dose	Ib	(see text for recommendation)

Stage of syphilis	Therapy	Level of evidence	Grading of recommendation
Late latent syphilis, cardiovascular and gummatous syphilis	Benzathine penicillin 2.4 million units IM weekly for 2 weeks (day 1, 8,15)	III	B
Late latent syphilis, cardiovascular and gummatous syphilis	Procaine penicillin 600.00 units IM for 17-21 days	III	B
Late latent syphilis, cardiovascular and gummatous syphilis	Doxycycline 200mg daily (either 100mg twice daily or as a single 200mg dose) for 21-28 days	IV	C
Late latent syphilis, cardiovascular and gummatous syphilis	Tetracycline 500mg 4x orally for 28 days	IV	C
Late latent syphilis, cardiovascular and gummatous syphilis	Erythromycin 500mg 4x daily for 28 days	IV	C

Stage of Syphilis	Therapy	Level of Evidence	Grading of Recommendation
Neurosyphilis and ocular syphilis	Benzyl penicillin 18-24 million units IV daily, as 3-4 million units every 4 hours for 10-21 days	III	B
Neurosyphilis and ocular syphilis	Benzyl penicillin 0.15 million units/kg/day IV over 6 doses (every 4 hours) for 10-14 days	III	B
Neurosyphilis and ocular syphilis	Procaine penicillin 1.2-2.4 million units IM daily PLUS Probenecid 500mg 4x daily, for 10-14 days	IIb	B
Neurosyphilis and ocular syphilis	Doxycylcline 200mg twice daily orally for 28 days	IV	C

Stage of Syphilis	Therapy	Level of Evidence	Grading of Recommendation
Early syphilis in pregnancy (primary, secondary and early latent syphilis)	Benzathine penicillin 2.4 million units IM as a single dose	IIb	B
Early syphilis in pregnancy (primary, secondary and early latent syphilis presenting in the last trimester of pregnancy)	Benzathine penicillin 2.4 million units 2 doses (day 1 and day 8)	III	B
Early syphilis in pregnancy (primary, secondary and early latent syphilis)	Procaine penicillin 600,000 units - 1.2million units IM daily for 10-14 days.	III	B

Stage of Syphilis	Therapy	Level of Evidence	Grading of Recommendation
Congenital syphilis	Benzyl penicillin 150,000 units/kg IV daily (administered in 6 doses every 4 hours) for 10-14 days	IV	C
Congenital syphilis	Procaine penicillin 50,000 units/kg IM daily for 10-14 days	IV	C
Congenital syphilis (if CSF examination is normal)	Benzathine penicillin 50,000 units/kg IM as a single dose	IV	C

Levels of evidence and grading of recommendations

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.
Ib Evidence obtained from at least one randomised controlled trial.
IIa Evidence obtained from at least one well designed study without randomisation.
IIb Evidence obtained from at least one other type of well designed quasi-experimental study.
III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Evidence levels Ia, Ib) Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III) Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence IV) Requires evidence from expert committee reports
or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.