European Dermatology Forum

Guideline on the Management of Syphilis

Developed by the Guideline Subcommittee "Syphilis" of the
European Dermatology Forum

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ORIGINAL ARTICLE

2014 European guideline on the management of syphilis

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Abstract

Background Syphilis remains a major public health problem in Europe (both in Eastern Europe since the 1990's and in Western Europe since the re-emergence of the disease in the late 1990's-early 2000's).

Methods This guideline is an update of the IUSTI: 2008 European guideline on the management of syphilis and is produced by the European Guideline Editorial Board (http://www.iusti.org/regions/Europe/pdf/2013/Editorial_Board.pdf) and EDF Guideline Committee.

Results It provides recommendations concerning the diagnosis and management of syphilis in Europe. Major advances include (1) broader use of PCR, immunohistochemistry, subtyping of the etiological agent *Treponema pallidum subspecies pallidum*, new treponemal tests, and rapid-point-of-care (POC) tests detecting both treponemal and non-treponemal antibodies, (2) more flexible options for screening (TT-*treponemal test*- first or NTT –*non treponemal test*- first or both TT and NTT), and (3) procaine penicillin is no longer the first line therapy option in any phase of the disease, i.e. long acting penicillin G (i.e. benzathine penicillin G-BPG) is the only first line therapy regimen in early syphilis and in late latent syphilis.

Conclusions Syphilis is a disease that is relatively easy to detect by appropriate serological tests, however, all laboratory results should be considered together with clinical data and sexual risk anamnesis. Syphilis is also easy to treat with BPG. A major concern about the supply of BPG in many European countries could threaten the efficacy of the policies of eradication of the disease in Europe.

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Introduction

Syphilis is a systemic human disease due to *Treponema pallidum subsp pallidum* (*T. pallidum*) and classified as acquired or congenital. Acquired syphilis (usually by sexual contact) is divided into early and late syphilis. Early syphilis includes primary, secondary and early latent syphilis. The European Centre for Disease Prevention and Control (ECDC) defines early syphilis (infectious syphilis) as syphilis acquired ≤1 year previously and the World Health Organisation (WHO) as syphilis acquired ≤2 years previously.[1,2] Late syphilis includes late latent and tertiary syphilis (gummatous, cardiovascular and neurosyphilis). The ECDC defines late syphilis as syphilis acquired >1 year previously and the WHO as syphilis acquired >2 years previously.[1,2] Congenital syphilis is divided into early (first 2 years) and late, including stigmata of congenital syphilis.

This guideline is an update of the 'IUSTI: 2008 European Guidelines on the Management of Syphilis'.[3]

Case finding

Routine tests for syphilis should be taken in all pregnant women, people donating blood, blood products or solid organs and the following groups at higher risk of syphilis: all patients who are

newly diagnosed with sexually transmitted infection (STI); persons with HIV; patients with hepatitis B; patients with hepatitis C; patients suspected of early neurosyphilis (i.e. unexplained sudden visual loss, unexplained sudden deafness or meningitis); patients who engage in sexual behaviour that puts them at higher risk (e.g. men who have sex with men (MSM), sex workers and all those individuals at higher risk of acquiring STIs). Screening tests should also be offered to all attendees at dermatovenereology/genitourinary medicine (GUM)/STI clinics afterwards referred to as 'sexual health clinics'.

Diagnosis

Clinical

Definition of stages is clinical, chronology begins with onset of chancre. Stages are overlapping. Secondary syphilis develops in one-third of untreated patients, tertiary syphilis in 10%. Patients are considered infectious to others through social (rarely) and sexual contact mainly in the first year (primary and secondary syphilis). Later transmission usually by other means (vertically and through tissue donation) is well described.

Incubation period: 10–90 days between contact (mostly sexual) and chancre.

Primary syphilis: an ulcer (chancre), usually with regional lymphadenopathy. The ulcer is primarily superficial, single, painless and indurated with a clean base discharging clear serum, most often in the anogenital region. It is never blistering in appearance. Lesions are often atypical in appearance and may be multiple, painful, deep and indistinguishable from herpes.[4–6] Any anogenital ulcer should be considered syphilitic unless proven otherwise. Chancres are frequently difficult to find in females and MSM. Initial tests may not allow a firm and conclusive rejection of a syphilis diagnosis and retesting with serology at 1, 2 and 6 weeks is needed to exclude a diagnosis – however, delaying treatment is hazardous in some populations especially when patients are unlikely to return for follow-up and thorough investigations.

Secondary syphilis: multisystem involvement due to bacteriaemia, within the first year but may recur up into the second year after infection. Usually non-itching skin rash (roseola in the 2–3 months after onset of chancre and papular syphilids later on) and/or mucocutaneous lesions are present in 90% of cases. Fever, generalized lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis and glomerulonephritis are possible.[7–11] Meningitis, cranial nerve palsies, auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papillar oedema), meningovascular syphilis (stroke, myelitis) can occur in secondary syphilis and should be individualized as early neurosyphilis.

Latent syphilis: positive serological tests for syphilis with no clinical evidence of treponemal infection. Rather arbitrarily classified as early if within the first year of infection and late (or undetermined duration) after >1 year. Early latent syphilis is a descriptive term that includes patients with positive serological tests for syphilis: a negative syphilis serology within 1 year of a syphilis diagnosis OR a fourfold (two dilutions) or greater decrease in Non-treponemal antibodies titre OR unequivocal evidence that the disease was acquired in the past year (on the basis of clinical signs in patient and partners).[12]

Tertiary syphilis:

- Gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)
- Late neurosyphilis encompasses meningitis, cranial nerve dysfunction, meningovascular syphilis (stroke, myelitis) and parenchymatous neurosyphilis (general paresis, tabes dorsalis)
- Cardiovascular syphilis: aortic regurgitation, stenosis of coronary ostia,[5] aortic aneurysm (mainly thoracic)

Neurologic syphilis: meningitis, cranial nerve dysfunction, can occur early (secondary syphilis) or late (tertiary syphilis) in the course of the disease.

Laboratory

Demonstration of T. pallidum

- Direct detection methods provide definitive diagnosis of syphilis.
- Darkfield examination (DFE) of chancres and erosive cutaneous lesions, gives immediate results but the method is laborsome, subjective and is subject to both false positive and (many) false negative results.[13,14]
- Polymerase chain reaction (PCR), preferred method for oral and other lesions where contamination with commensal treponemes is likely; can be performed in tissues, cerebrospinal fluid (CSF), blood (although insensitive in the latter), etc.[14–20] There is no internationally approved PCR for *T. pallidum* and accordingly, it is crucial to select a strictly validated method and always use it with appropriate quality controls.
- Algorithms for DFE and PCR for exact clinical situations are heavily dependent on local expertise and laboratory setups – they are currently outside the scope of this guideline.
- Immunohistochemistry using a polyclonal antibody against *T. pallidum* can be efficient to identify treponemes in skin, mucosal and tissue lesions.[19,20]
- Hybridization in tissues
- Warthin–Starry (argentic) staining on tissues is very difficult to perform and unhelpful in most cases.
- Subtyping of *T. pallidum* by PCR-restriction fragment length polymorphism (RFLP) and/or DNA-sequencing can be performed on clinical specimens, however, the discriminatory ability of this subtyping is low (subtype 14d predominates in Europe and mainly worldwide).[21–24]

- (The Direct fluorescent antibody test is now considered obsolete)

Serological tests for syphilis (STS)[14,25–37]

STS provide a presumptive diagnosis of syphilis.

None of the STS differentiate between venereal syphilis and the non-venereal treponematoses (yaws: *T. pallidum subsp pertenue*; bejel – endemic syphilis: *T. pallidum subsp endemicum* and pinta: *T. carateum*). These pathogens are morphologically and antigenically similar, and can be differentiated only by their mode of transmission, epidemiology, clinical manifestations, and more recently, at least some of the pathogens with DNA sequencing.[38] A person with positive STS should be investigated and treated as for syphilis as a precautionary measure unless previously adequately treated syphilis is documented.

- Non-treponemal tests (NTT): using a complex antigen consisting of cardiolipin, lecithin and cholesterol (lipoidal tests, reagin tests) such as the Venereal Diseases Research Laboratory test (VDRL), the Rapid Plasma Reagin test (RPR), the Toluidine Red Unheated Serum Test (TRUST), etc. All these tests detect a mixture of heterophile IgG and IgM, are manual and not automatizable, but they are cheap, simple and, if appropriately performed, have a relatively high sensitivity. NTT become positive 10–15 days after the beginning of the primary chancre (i.e. around 6 weeks after infection). In the absence of treatment, the titre reaches a peak between 1 and 2 years following infection and remains positive with low titres in very late disease.[14] Spontaneous seroreversion of NTT along with tertiary syphilis is extraordinarily rare (if it exists). Titres of NTT grossly correlate with disease activity, results should be reported quantitatively, and as such are used to monitor disease activity and efficacy of treatment.
- Treponemal tests (TT): *T. pallidum* Haemagglutination test (TPHA), Micro-Haemagglutination Assay for *T. pallidum* (MHA-TP), *T. pallidum* Passive Particle Agglutination test (TPPA), Fluorescent Treponemal Antibody absorption test (FTA-abs test), Treponemal Enzyme Immunoassay (EIA), Chemiluminescence Immunoassay (CIA), IgG immunoblot test for *T. pallidum*. Most of these tests use recombinant treponemal antigens and detect both IgG and IgM. FTA-abs test is becoming obsolete because it is time-consuming, expensive and difficult to read. TPHA and TPPA are manual and subject to individual variations in interpretation, but they are cheap and widely used all over Europe. EIA and CIA tests are automated but are often expensive and suboptimally evaluated and standardized.[14] Tests become positive in the 1st–2nd weeks of the chancre. Titres of TT are not helpful in the diagnosis or management of syphilis (with possible exception of congenital syphilis). TT should not be used to assess disease activity and treatment outcome and remain positive for life in most patients.[14]
- Specific anti-*T. pallidum* IgM antibody tests: EIA/IgM, 19S-IgM-FTA-abs test, IgM-immunoblot for *T. pallidum*. The sensitivity of such tests is low in active syphilis. IgM does not help to stage syphilis accurately and should not be relied upon to determine lengths of treatment. IgM's main usefulness is in the assessment of newborns and CSF.[14]
- Many rapid Point of Care (POC) tests using treponemal antigens have been developed in the last 20 years. Initially tests had suboptimal sensitivity compared to traditional methods, but some of the latest assays have shown a substantially improved sensitivity.[35,39] However, these tests did not detect cardiolipin antibodies (i.e. patients with active infectious syphilis). New POC tests have substantially better performances for detection of both Treponemal and Non-treponemal antibodies.[40–44] Use of rapid POC tests is very important in the WHO strategy for global elimination of congenital syphilis and mother-to-child-transmission (MTCT) of both syphilis and HIV, because they permit screening and treatment at the same visit at field level or peripheral clinics remote from laboratories. Currently, where laboratory diagnostics is available for syphilis in Europe syphilis POC tests are not recommended for use.

Primary screening test(s)[3,14,35–37,45,46] *(Table 1)*

- A TT [TPHA, MHA-TP, TPPA or EIA/CIA]. This screening algorithm, using by preference an automatized EIA/CIA, is used in many larger European laboratories within more resourced settings and is particularly suitable for automated high-throughput screening of asymptomatic populations and blood/plasma donors. The algorithm identifies persons with previous successful treatment of syphilis as well as persons with untreated syphilis. It is better able to detect very early syphilis compared to the use of a screening NTT. However, it can also result in a high number of false positive tests (low positive predictive value) in low-prevalence populations.
- A NTT [RPR or VDRL], which is ideally quantitative (i.e. to detect prozone phenomenon in infectious syphilis), is still recommended in the USA and some European countries. In this algorithm, only active (infectious) syphilis is detected. It can miss very early syphilis more often than TT.

Table 1 Syphilis screening in Europe

Primary screening test
Option 1: a TT (TPHA, MHA-TP, TPPA or EIA/CIA)
Option 2: a NTT (ideally quantitative) (RPR or VDRL)
Option 3: both a TT and a NTT
Confirmatory test(s) on the same serum if any screening test is positive
Option 1: another TT of a different type AND a quantitative NTT if second TT is positive
Option 2: a TT
Option 3: NTT must be performed quantitatively

- Both a TT and a NTT. This algorithm is wise in case of suspicion of very early syphilis (recent chancre, contacts of syphilis cases etc.).

Confirmatory test(s) if any screening test is positive[3,14,35–37,45,46] *(Table 1)*

Although confirmation of a positive TT and ruling out a false positive test may be important for counselling, notification and have a psychological impact, it has limited impact on treatment.

- In the case a TT alone is used as a primary screening test, if positive, use another TT (of a different type) as confirmatory test on the first serum (e.g. TPPA/TPHA if EIA/CIA is used for screening or EIA/CIA if TPHA/TPPA is used for screening) and add a quantitative NTT in all cases when the second TT is positive. When the confirmatory TT test is positive and NTT is negative, in patients with suspicion of early syphilis, an EIA-IgM test may be used although treatment should be administered in all cases.
- In the case a NTT alone is used as a primary screening test, a positive test must be followed by a TT and if not initially done, the NTT should be performed quantitatively.
- In the case both TT and NTT are used as primary screening tests such as (TPHA/TPPA and VDRL/RPR), NTT must be performed quantitatively (particularly if TT is positive). A confirmatory test (EIA/CIA or immunoblot) may be used to rule out a false positive TT only if the NTT is negative, although this has no practical impact (i.e. it is recommended to still treat a patient with negative NTT in case of suspicion of early syphilis, e.g. genital ulceration, and in case of an asymptomatic patient with persistently negative NTT treatment is mostly not initiated).
- IgG-immunoblot for *T. pallidum* has no added major value to other TT. It is expensive and interpretation of undetermined immunoblot is elusive (1–4 bands).

Tests for serological activity of syphilis and for monitoring the effect of treatment

- Quantitative VDRL or RPR tests may both be used for monitoring the disease progression and effectiveness of treatment at follow-up visits.
- Titre must be obtained on the very first day of treatment, that is, to provide a baseline for measuring a decrease in antibody titres.
- Serum should be obtained at 1, 3 and every 6 months subsequently, ideally the identical NTT should be used and all samples tested in the same laboratory. This should be continued until the NTT becomes negative, attains a low plateau (1 : 1–1 : 4, sustained for 1 year and in the absence of ongoing risk) [**IV**; **C**; see Appendix]. Patients with higher titres should remain under follow-up.

Laboratory: false negative syphilis serology[3,14,25,26].

- All STS (TT and NTT) are negative before appearance of chancre and in the first 5–15 days of the chancre. Discordance can be as follows: positive TT/negative NTT (2/3 of cases in primary syphilis) or negative TT/positive NTT (1/3 of cases in primary syphilis). A negative NTT (or attained at a low plateau, see above) along with a positive TT is a rule in treated and cured syphilis. However, in late syphilis NTT frequently remain positive despite provision of adequate treatment. A negative NTT is the best criterion for an adequately treated syphilis.
- A false negative TT in the course of the disease is exceedingly rare and can usually be explained by technical problems or mix up of samples.
- A false negative NTT (along with positive TT) may occur in particularly early syphilis due to the prozone phenomenon (excess of antibodies) when using undiluted serum. Dilution of serum for NTT must be performed in each case of a positive TT.
- A false negative NTT has also been described in old textbooks in active (very) late-stage syphilis (Bordet–Wassermann reaction). This is an extraordinarily rare situation, if it even exists.[47]
- Temporarily negative NTT and TT (reactive on subsequent testing) have occasionally been reported in secondary syphilis (so-called malignant syphilis). Diagnosis can rely on DFE, *T. pallidum* PCR, histology and histochemistry.
- Retesting both TT and NTT is necessary on a second serum in case of discordance in an asymptomatic patient. In case of chancre (ideally proven by DFE or PCR positivity) treatment should be administered in all cases (positive TT/NTT; Discordant TT/NTT and negative TT/NTT) to cover the possibility that the patient may not return for follow-up results or delayed therapy.

Laboratory: false positive syphilis serology[3,14,25,26,48].

- Biological false positive (BFP) NTT results are associated with various medical conditions and have been estimated to occur in 0.2%–0.8% of tests (and even higher in some studies). They can be divided as acute (≤6 months) and chronic (>6 months). Acute BFP may be seen in postimmunization, recent myocardial infarction and in many febrile infective illnesses (e.g. malaria, hepatitis, chicken pox, measles, etc.), and possibly in pregnancy. Chronic BFP may be seen in injecting drug users, autoimmune diseases, HIV infection and chronic infections such as leprosy, malignancies, chronic liver pathology and older age. Occasional BFP TT tests (FTA-abs test more than TPHA/MHA-TP/TPPA) may be seen in autoimmune diseases, and during pregnancy and can be excluded with the IgG immunoblot test for *T. pallidum*. The majority of BFP NTT sera show antibody titres of ≤1:4. A positive

NTT must be retested on a subsequent serum along with a TT.
- BFP TT results are occasionally seen in connective tissue disorders, and Lyme disease, particularly the FTA-abs test. All TT with visual assessment (FTA-abs test, TPHA, TPPA, etc) are subject to false-positive reactions for low titres of antibodies. Retesting on a subsequent serum is necessary in case of negative NTT.

Laboratory tests to confirm or exclude neurosyphilis[49–59]

A complete clinical examination (neurological, ocular and otologic) must be completed in every patient with positive STS. However, in those without symptoms it is rarely contributory.[60]
- Fundoscopy must be performed before lumbar puncture (LP). Computer tomography (CT) of the brain should be requested if neurological problems are identified.
- CSF assessment is not indicated in early syphilis (HIV positive or negative[61]), unless there are neurological, ocular or auricular symptoms.
- CSF assessment is indicated in patients with:
  - clinical evidence of neurological, ocular and auricular involvement, whatever the stage of the disease
  - tertiary syphilis (cardiovascular, gummatous)
- Definition of asymptomatic neurosyphilis is extremely difficult and contentious. Most definitions depend on a combination of CSF laboratory tests (protein, cells, CSF TT and CSF NTT) but no consensual definition exists.
- Although penicillin levels after injection of benzathine penicillin G (BPG) are frequently under the reputed penicillin treponemicidal level, progression from asymptomatic to symptomatic neurosyphilis is extraordinarily rare. As CSF assessment is not without its own dangers, LP investigation is not recommended in the vast majority of asymptomatic patients.
- Although robust data are lacking, CSF control may be indicated also in asymptomatic patients in the following situations for exclusion of asymptomatic neurosyphilis:
  - in HIV positive patients with late syphilis AND CD4+ cells $\leq$350/mm^3 AND/OR a serum VDRL/RPR titre >1:32
  - in case of serological failure
  - in case of use of alternative treatment (tetracyclines) during late syphilis
- Examination of CSF: must include total protein, number of mononuclear cells, a TT (TPHA/MHA-TP/TPPA) and a NTT (VDRL (preferably used)/RPR)
  - Normal protein level is possible in neurosyphilis.
  - The number of mononuclear cells in CSF can be normal in neurosyphilis, especially in parenchymatous neurosyphilis (tabes dorsalis, general paresis).[49,50] Conversely, high number of mononuclear cells in CSF can be observed in a number of situations, including HIV infection in the absence of syphilis.
  - A positive CSF VDRL test is observed in only about 1 : 3 cases of neurosyphilis but a positive test can in the absence of substantial blood contamination be considered as indicative of neurosyphilis in late syphilis. However, in early syphilis the significance of a positive CSF VDRL test is less clear.
  - A positive CSF TT (TPHA/TPPA) does not confirm the diagnosis of neurosyphilis but a negative CSF TT result is highly unlikely in neurosyphilis.[11]
  - Several indexes taking into account blood–brain barrier (albumin) aiming at evaluation of intrathecal synthesis of immunoglobulins have been produced, however, none have been of real practical use.
- CSF PCR for the presence of *T.pallidum* to help establish a diagnosis of neurosyphillis is currently considered of little value since tests to date have shown low sensitivity and specificity.[16,17]
- In case of an abnormal CSF examination (high protein level and/or hypercytosis), repeat CSF examination must be performed after treatment (6 weeks–6 months).

Investigation for cardiovascular syphilis
- Any patient with aortic insufficiency or thoracic aortic aneurysm should be screened for syphilis.
- Auscultation must be performed in patients with late latent or tertiary syphilis. A chest X-ray is rarely contributory.[62]

Investigation for ocular syphilis
- Any patient with unexplained sudden visual loss should be screened for syphilis.
- Clinical ocular assessment must be performed in patients with secondary, early latent, tertiary and late latent syphilis, and a fundoscopy performed if any clinical ocular sign is found.
- Performing CSF examination is controversial as intraveneous (IV) penicillin therapy will be initiated anyway, there are reasons why this may be helpful – in many patients it will exclude other pathologies in the differential diagnosis and if found to be abnormal in someone with neurosyphilis requires appropriate follow-up to ensure all markers return to acceptable levels.

Investigation for auricular syphilis
Any patient with unexplained sudden hearing loss should be screened for syphilis.

Management
Individuals with syphilis are at higher risk of acquiring other STIs. All patients with syphilis should be tested for HIV and HCV if risk factors (as assessed by local epidemiology are present). All individuals with syphilis should have a full

STI assessment. Assessment and vaccination for Hepatitis B should also be considered as appropriate.

General remarks[63–69]

- A treponemicidal level of antimicrobial should be achieved in the serum, and in the case of neurosyphilis also in the CSF. A penicillin level of >0.018 mg/L is considered treponemicidal, but this level is substantially lower than the maximally effective *in vitro* level of concentration (0.36 mg/L).
- Duration of treponemicidal level of antimicrobials should be at least 7–10 days to cover a number of division times (30–33 h). Longer duration of treatment is needed as the duration of infection increases (more relapses have been 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.[64] The significance of this finding, if any, remains unknown.
- In general, long acting BPG 2.4 million units is the treatment of first choice, which provides a treponemicidal penicillin level in blood for up to 21–28 days. 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 all antimicrobials, even for penicillin.
- Treatment recommendations are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinions, case studies and past clinical experience.
- Parenteral rather than oral penicillin treatment is the treatment of choice because parenteral therapy is supervised with guaranteed bioavailability. However, amoxicillin, given orally in combination with probenecid appears to be effective and results in treponemicidal drug levels within the CSF.[69]
- Non-penicillin antibiotics have been evaluated. These include tetracyclines, (doxycycline, is the preferred tetracycline with good penetration into the CSF), and erythromycin, both taken orally.[70] Erythromycin is less effective and does not penetrate the blood–brain or placental barrier well. Newer antitreponemals include intramuscular or intravenous ceftriaxone.[71,72] Ceftriaxone has good CSF penetration, but it requires multiple injections, dose and duration are not standardized and it does not offer any advantages to single dose BPG.[73] However, like oral doxycycline, daily ceftriaxone injected intravenously or subcutaneously may be an alternative in patients with bleeding disorders.

  In case of penicillin allergy, use of ceftriaxone may be an option with risk although cross allergies are not frequent. History of anaphylaxis is an absolute contraindication.[45]

  Azithromycin has shown good treponemicidal activity in animal studies and several controlled studies, mostly in Africa. However, resistance to azithromycin can easily develop and clinical failures have been described in several studies.[23,74–79]
- The host immune response is important as 60% of untreated patients will not develop clinical features other then primary lesions.[80] CSF involvement is common in early syphilis.[49,57] Although both parenteral BPG and standard regimens of parenteral procaine penicillin do not achieve treponemicidal CSF levels,[51,58] 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.
- BPG is widely used because of efficacy and ease of treatment. Replacing part of solvent by the same volume of 1% lidocaine solution may reduce the pain associated with injection[81] and in late syphilis may improve compliance for the second and third injection. Compliance with daily intramuscular injections with procaine penicillin has been shown to be good in the United Kingdom.[82] The control of syphilis over the past 50 years has been excellent compared to the prepenicillin era. Late complications of syphilis and/or failures of treatment are uncommon, even in patients with concomitant HIV infection.
- There is no established relationship between immune-suppression and the severity of syphilis related disease. However, a closer follow-up (i.e. 1, 3, 6, 9 and 12 months) can be recommended in HIV-positive patients, particularly if the CD4+ cell count is $\leq 350/mm^3$ and/or if the patient is not treated with antiretroviral therapy.

  HIV coinfection does not appear to increase the risk of developing a more aggressive course of early syphilis.[61] Modest differences have been published with a slightly higher prevalence of: (i) multiple chancres; (ii) concomitant chancre and secondary eruption and (iii) Herxheimer reaction, in patients infected with HIV. Risk of ocular and neurological involvement is not increased in HIV positive patients with early syphilis. Thus, CSF examination in early syphilis is indicated only in patients with overt ocular, auricular or neurologic symptoms, (for the same reasons as in non-HIV-infected patients).[45,46,57] Data are lacking in late syphilis. Some specialists recommend routine-CSF examination in HIV-positive patients with late syphilis to exclude asymptomatic neurosyphilis, although there are no robust data to support it. Some experts limit the indications of CSF examination to HIV positive patients with late syphilis AND CD4+ cells $\leq 350/mm^3$ AND/OR a serum VDRL/RPR titre >1 : 32,[56] although there are no robust data to support it.

Table 2 Treatment of syphilis in Europe

Early syphilis (Primary, Secondary and Early latent, i.e. acquired ≤1 year previously)
First line therapy option
Benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM) (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 [Ib; A]
Penicillin allergy or parenteral treatment refused
Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [III; B]
or azithromycin 2 g orally single dose [I; B]
Late latent (i.e. acquired >1 year previously or of unknown duration), cardiovascular and gummatous syphilis
First line therapy option
Benzathine penicillin G (BPG) 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on day 1, 8 and 15 [III; B]
Penicillin allergy or parenteral treatment refused
Desensitization to penicillin
or doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21–28 days [III; B]
Neurosyphilis, ocular and auricular syphilis.
First line therapy option
Benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 h during 10–14 days [III; B]
Second line therapy option (if hospitalization and IV benzyl penicillin is impossible)
Ceftriaxone 1–2 g IV daily during 10–14 days [III; B]
Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both during 10–14 days [IIb; B]
Penicillin allergy
Desensitization to penicillin followed by the first line regimen [III; B]
Syphilis in pregnancy
Pregnant women should be treated with the first line therapy option appropriate for the stage of syphilis and if allergic to penicillin should be desensitized.
Syphilis in HIV
Treatment should be given as for non-HIV infected patients, although there are very few data on the use of second line options

Recommended treatment regimens[2,3,46,54,61,83] (Table 2)

Early syphilis (Primary, Secondary and Early latent, i.e. acquired ≤1 year previously)

First line therapy option.

- Benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM) (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 [**Ib; A**]
  Replacing part (i.e. 0.5–1 cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection.[84] This is not feasible in case of premounted BPG syringes.
  Patients should be kept for 30 min clinical review after injection.

Second line therapy option.

- Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available [**IIb; B**]

Bleeding disorders.

- Ceftriaxone 500 mg–1 g subcutaneously or IV daily for 10 days [**III; B**]
- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [**III; B**]
- Azithromycin 2 g oral single dose [**I; B**]

Penicillin allergy or parenteral treatment refused.

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [**III; B**]
- Azithromycin 2 g orally single dose [**I; B**]

Late latent (i.e. acquired >1 year previously or of unknown duration), cardiovascular and gummatous syphilis

First line therapy option.

- Benzathine penicillin G (BPG) 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on day 1, 8 and 15 [**III; B**]
  Replacing part (i.e. 0.5–1 cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection. This is not possible in case of premounted syringes.
  Patients should be kept for 30 min clinical surveillance after injection.

Second line therapy option.

- Procaine penicillin 600 000 units IM daily during 17–21 days, i.e. if BPG is not available [**III; B**]

Penicillin allergy or parenteral treatment refused.

Some specialists recommend penicillin desensitization as the evidence base for the use of non-penicillin regimens is weak.

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21–28 days [**III; B**]

Neurosyphilis, ocular and auricular syphilis

- Regimens that achieve treponemicidal levels of an antibiotic in the CSF should be the treatment of choice: IV therapy is the best option.
- Other regimens with weaker evidence can achieve treponemicidal levels in the CSF, i.e. the procaine penicillin/probenecid combination and ceftriaxone (IV or IM). The availability of probenecid may also be a problem.
- Early ocular syphilis such as uveitis syphilitica of short duration may be successfully treated with BPG, but this option is not recommended.

First line therapy option.

- Benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 h during 10–14 days [**III; B**]

Second line therapy option.

If hospitalization and IV benzyl penicillin is impossible

- Ceftriaxone 1–2 g IV daily during 10–14 days [**III; B**]
- Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both during 10–14 days [**IIb; B**]

Penicillin allergy.

- Desensitization to penicillin followed by the first line regimen [**III; B**]

Special considerations

Pregnancy

In pregnant women with untreated early syphilis, 70%–100% of infants will be infected, with stillbirths in up to one-third of cases.[85,86]

Women with persistently negative NTT results are very unlikely to transmit syphilis during pregnancy.[87] Most transmissions to the fetus occur after 20 weeks and treatment before this period will usually prevent congenital features.[85] 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. Pregnant women with penicillin allergy should be desensitized and treated with penicillin.

First line option for treatment of early syphilis (i.e. acquired ≤1 year previously).

- Benzathine penicillin G (BPG) 2.4 million units IM single dose (or 1.2 million units in each buttock) [**I; B**]
  Note: some specialists recommend two doses of BPG 2.4 million units (day 1 and 8) but this is not sufficiently evidence based.[88–90]
  Patients should be kept for 30 min clinical review after injection.

Second line therapy option.

- Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available [**III; B**]

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

- Recommendation: all pregnant women should be screened at first antenatal visit (first trimester). Serology should be repeated in case of high risk and local epidemiology.
- Some specialists recommend that all infants born to syphilis seropositive mothers should be treated with a single dose of BPG 50.000 units/kg IM, whether or not the mother was treated during pregnancy.

Congenital syphilis[85,86,91]

Confirmed congenital infection.

- *T. pallidum* demonstrated by DFE or PCR in placenta or autopsy material, exudate from suspicious lesions or body fluids, e.g. nasal discharge.

Presumed congenital infection.

- A stillborn neonate with a positive treponemal test for syphilis.
- Children with a positive treponemal test for syphilis in combination with one or several 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 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 and in whom sexual abuse has been excluded.

Late congenital syphilis.

- Interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, rhagades, deafness, frontal bossing, short maxilla, protuberance of mandible, saddlenose deformity, sternoclavicular 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 cases of congenital syphilis must be reported to the national Syphilis Surveillance system where required by local mandate.

Investigations.

- RPR/VDRL, TPPA/TPHA (quantitative), anti-treponemal IgM-EIA, treponemal IgM (19S-IgM FTA-abs or IgM-immunoblot) – from infant's blood and not umbilical cord blood, because false-positive and false-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

First line therapy option.

- Benzyl penicillin 150 000 units/kg IV daily (administered in six doses every 4 h) during 10–14 days [**IV; C**]
- If CSF is normal: check for age

a First line therapy: BPG 50 000 units/kg IM (single dose) up to the adult dose of 2.4 million units [**IV; C**]

b Second line therapy: Procaine penicillin 50 000 units/kg IM daily for 10–14 days, i.e. if BPG is not available [**IV; C**]

HIV-infected patients

General remarks[60,61,92–97]

- Serological tests for syphilis in patients with HIV coinfection are generally reliable for the diagnosis of syphilis and for evaluation of treatment response.
- Patients with HIV coinfection may have a slower rate of decline of VDRL/RPR after treatment, but this should not be considered as failure of response to treatment.
- False-negative and false-positive tests and delayed appearance of seroreactivity have been reported but are anecdotal.
- In HIV-infected individuals with clinical suspicion of syphilis and negative syphilis serology (repeatedly), 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 DFE or PCR of the exudate of early syphilitic lesions for treponemes.[45]
- HIV-infected patients with early syphilis do not appear to have an increased risk of (early) neurological and ocular involvement or higher rate of treatment failure with BPG.
- No data are available concerning the risk of neurosyphilis in HIV-infected patients with late syphilis, however, some specialists recommend CSF examination as part of the assessment of HIV-infected patients with late-latent syphilis (or syphilis of unknown duration).

Treatment of syphilis in patients with concomitant HIV infection.

- Treatment should be given as for non-HIV-infected patients, although there are very few data on the use of second line therapy options.
  Note: Careful follow-up is essential.

Syphilis induced by solid organ transplant

First line therapy options.

- Benzathine penicillin G (BPG) 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on day 1, 8 and 15 [**III; B**][98]

Penicillin allergy.

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21–28 days

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 h.
- Common in early syphilis but is usually not important unless there is neurological or ophthalmic involvement, in neonates 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 prevent the febrile episode[99] Although steroids are unproven at ameliorating local infection, biological plausibility suggests that those may help preventing severe deterioration in early syphilis with optic neuritis and uveitis.
- Management:
  - If cardiovascular or neurological involvement (including optic neuritis) exists, inpatient management is advisable.
  - Prevention of Jarisch–Herxheimer reaction: Prednisolone 20–60 mg daily for 3 days, starting antitreponemal treatment after 24 h of commencing prednisolone [**IV; C**]
  - Antipyretics

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

- Due to inadvertent IV injection of procaine penicillin and 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 min.
- Management:
  - Exclude anaphylaxis
  - Calm and verbal reassurance; restraint may be necessary.
  - Diazepam 5–10 mg rectally/IV/IM if convulsions

Anaphylactic shock.

- Facilities for treatment of anaphylaxis should be available as penicillin is one of the most frequent 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

Contact tracing, management of sexual partners and notification of syphilis cases

- All patients with syphilis should be seen for sexual contact notification (notification by the patient: patient referral; by a health department: provider referral), health education and confirmation of any past treatment history. Exact advice from International Union against STI (IUSTI) on this matter can be found in the IUSTI guideline on Partner management at http://www.iusti.org/regions/Europe/euroguidelines.htm
- Clear information, ideally written such as the IUSTI leaflet, should be given to all individuals with syphilis and their sexual contacts. Patient information resources can be found at http;//www.iusti.org/regions/Europe/PatientInformation.htm
- Sexual contact notification assists community efforts to reduce the disease burden, helps to identify asymptomatic syphilitic patients and can delineate the sexual risk networks hosting transmission. Contact notification programs in outbreaks associated with a high rate of untraceable contacts need to adopt innovative approaches to partner notification, including use of the internet and community outreach programs.
- Sexual contacts 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 contacts within the past 3 months should be notified as the incubation period is up to 90 days. Partner notification may have to extend up to 2 years for patients in secondary syphilis with clinical relapse or in early latent syphilis. Longer periods may be required in those with late latent and late syphilis.
- 46%–60% of traced sexual contacts, including pregnant women, of patients with early syphilis are likely to be infected.
- Immediate epidemiological treatment for sexual contacts should be considered (especially of pregnant partners!) unless contacts are able to attend regularly for exclusion of syphilis through clinical and serological examination (0, 4 weeks and 3 months).
- 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 mandatory in most European countries, particularly early syphilis and congenital syphilis. The ECDC is responsible for the European Union-wide surveillance of communicable diseases including syphilis.

Follow-up and test of cure

Follow-up to ascertain cure and detect reinfection or relapse is achieved by assessing the clinical and serological response to treatment. Globally many studies confirm that follow-up is poor.[92,100]

- Early syphilis, minimum clinical and serological (VDRL/RPR) at 1, 3 months then at 6 and 12 months.
  - After treatment of early syphilis the titre of a NTT (e.g. VDRL and/or RPR) should decline by two dilution steps (fourfold) within 6 months.[1,3,14] However, about 15% or more patients with early syphilis and no HIV infection do not have a fourfold decrease of titre at 6 months, the significance of which is unknown.
  - If a fourfold decrease of the titre of a NTT does not occur after 6–12 months, some experts recommend additional treatment with one weekly injection of BPG 2.4 million units for 3 weeks [**IV; C**].
  - A negative NTT can be obtained in a substantial (but not in all) number of patients treated for early syphilis after 1–2 years. A negative NTT after treatment is considered as the best test of cure.
  - A TT may remain positive for life following effective treatment; proper documentation is necessary to prevent unnecessary retreatment.
- In late (latent) syphilis the serological response of NTTs is often absent. In non-HIV-infected late latent syphilis patients with a reactive NTT, which remains stable in the lowest titre range, follow-up after treatment is generally not indicated.
- An increase in ≥2 dilution steps (fourfold) in a NTT suggests reinfection or reactivation. Treatment should be given according to the above guidelines. Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.
- Follow-up examination of cerebrospinal fluid should be performed 6 weeks–6 months after treatment of neurosyphilis.[101]

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

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Appendix

Search strategy

This guideline has been updated from the IUSTI-Europe Syphilis guideline 2008.[3] Evidence for this guideline was provided by review of the Medline/Pubmed, Embase and Cochrane Library from 2008 to March 2014, using the term syphilis, neurosyphilis, congenital syphilis and *Treponema pallidum*.

Tables of level of evidence and grading of recommendation

Levels of Evidence	
Ia	Evidence obtained from meta-analysis of randomized controlled trials.
Ib	Evidence obtained from at least one randomized controlled trial.
IIa	Evidence obtained from at least one well-designed study without randomization.
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 randomized 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 randomized 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.