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GUIDELINES

2020 European guideline on the management of syphilis

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Abstract

The 2020 edition of the European guideline on the management of syphilis is an update of the 2014 edition.
Main modifications and updates include:

- The ongoing epidemics of early syphilis in Europe, particularly in men who have sex with men (MSM)
- The development of dual treponemal and non-treponemal point-of-care (POC) tests
- The progress in non-treponemal test (NTT) automatization
- The regular episodic shortage of benzathine penicillin G (BPG) in some European countries
- The exclusion of azithromycin as an alternative treatment at any stage of syphilis
- The pre-exposure or immediate post-exposure prophylaxis with doxycycline in populations at high risk of acquiring syphilis.

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Conflicts of interest

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Introduction

Syphilis is a systemic human disease due to *Treponema pallidum* subsp. *pallidum* (referred as *T. pallidum* below) and classified as acquired or congenital. Acquired syphilis (primarily 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 Organization (WHO) as syphilis acquired <2 years previously.[1,2] Late syphilis includes late latent and tertiary syphilis (gummatous, late cardiovascular and late 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 (mother-to-child-transmission of syphilis) is divided into early (first 2 years) and late, including stigmata of congenital syphilis. The incidence of syphilis in the European Union/European Economic area (EU/EEA) has shown an overall increase since 2000, which has been mainly due to a significant increase in Western and Central EU/EEA countries and particularly among men who have sex with men (MSM).[3]

This guideline is an update of the 2014 European guideline on the management of syphilis.[4]

Case finding (2, C)

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; persons on pre-exposure prophylaxis (PrEP); patients with hepatitis B and/or 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 places them at higher risk (e.g. MSM, sex workers and all those individuals at higher risk of acquiring STIs). Screening tests should also be offered to all attendees at dermato-venereology/genitourinary medicine (GUM)/STI clinics referred to hereafter as 'sexual health clinics'.

Table 1 Treatment of syphilis in adults

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
Second-line therapy option:
• Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available
Bleeding disorders:
• Ceftriaxone 1g intravenously (IV) daily for 10 days
• Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days
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
Late latent (i.e. acquired ≥1 year previously or of unknown duration), cardiovascular and gummatous syphilis
First-line therapy option:
• 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
Second-line therapy option:
• Procaine penicillin 600 000 units IM daily during 17–21 days, i.e. if BPG is not available
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.
Neurosyphilis, ocular and auricular syphilis
First-line therapy option:
• Benzyl penicillin 18–24 million units IV daily, as 3-4 million units every 4 hours for 10–14 day
Second-line therapy option:
• If hospitalization and IV benzyl penicillin is impossible
• Ceftriaxone 1–2 g IV daily for 10–14 days
• Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both for 10–14 days
Penicillin allergy:
• Desensitization to penicillin followed by the first-line regimen
Pregnancy
First-line option for treatment of early syphilis (i.e. acquired <1 year previously):
• BPG 2.4 million units IM single dose (or 1.2 million units in each buttock)
Second-line therapy option:
• Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available
Penicillin allergy.
• Desensitization to penicillin followed by the first-line regimen
HIV-infected patients
Treatment of syphilis in patients with concomitant HIV infection
• Treatment should be given as for non-HIV-infected patients.

Diagnosis

Clinical[5–9]

The definition of stages is clinical, chronology beginning with the onset of a chancre (ulcer or erosion). Stages can overlap. Secondary syphilis develops in approximately one-third of untreated patients, tertiary syphilis in about 10%. Patients are infectious primarily through 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.[10]

Incubation period: 10–90 days between infection and emergence of chancre.

Primary syphilis: a chancre, usually with regional lymphadenopathy. The chancre is typically superficial, single, painless and indurated with a clean base discharging clear serum, most often in the anogenital region. It is never blistering in appearance. Chancres are often atypical in appearance and may be multiple, painful, deep and indistinguishable from herpetic ulceration.[11–13] 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 the diagnosis – however, delaying treatment is hazardous in some populations especially when patients are unlikely to return for follow-up and thorough investigations.

Secondary syphilis[14–19]: multisystem involvement due to bacteriaemia, usually within the first year but it may recur in 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, aortitis and glomerulonephritis are possible. Meningitis, cranial nerve palsies, auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papillar oedema), meningo-vascular 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 (or non-primary non-secondary early syphilis)[6] is a descriptive term that includes patients with positive serological tests for syphilis *and:*

-a negative syphilis serology within 1 year of a syphilis diagnosis OR

-a fourfold (2 dilutions) or greater increase of non-treponemal antibodies titre within 1 year of previous testing OR

-unequivocal evidence that the disease was acquired in the past year (on the basis of clinical signs in patient and partners).[20]

Misclassification of early vs late latent syphilis is common.

Tertiary syphilis:

-Gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral);

-Late neurosyphilis encompasses meningitis, cranial nerve dysfunction, meningo-vascular syphilis (stroke, myelitis) and parenchymatous neurosyphilis (general paresis, tabes dorsalis);

-Cardiovascular syphilis: aortic regurgitation, stenosis of coronary ostia, 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 was the old gold standard method for definitive diagnosis. It gives immediate results. However, the method is labour-intensive and subjective and can result in some false-positive and (many) false-negative results.[21,22] Due to the availability of more sensitive and specific tests (specifically the PCR), it is not recommended for routine diagnosis anymore.
- Polymerase chain reaction (PCR) testing is the preferred method particularly but not exclusively for oral and other lesions where contamination with commensal treponemes is likely. It can be performed using tissues, cerebrospinal fluid (CSF) or blood (although insensitive in the latter).[22–28] There is no internationally approved PCR assay for *T. pallidum* and accordingly, it is crucial to select a strictly validated and quality-assured method and always use it with appropriate quality controls.
- Immunohistochemistry using a polyclonal antibody against *T. pallidum* can be efficient to identify treponemes in skin, mucosal and tissue lesions,[27,28] but it is not suitable for routine diagnosis.
- Hybridization in tissues[29] is not used for routine diagnosis.
- Warthin–Starry (argentic) staining on tissues is very difficult to perform and of limited value in most cases.
- As specialized supplies, equipment and training are required, the direct fluorescent antibody test is not recommended for routine diagnosis.
- For molecular epidemiological typing, PCR, PCR-restriction fragment length polymorphism (RFLP) and/or DNA sequencing (e.g. multilocus sequence typing (MLST) or whole genome sequencing) can be performed on clinical specimens. However, due to the highly conserved genome of *T. pallidum* the discriminatory ability of typing methods is in general low.[30–36]

Serological tests for syphilis (STS)[22,37–50] Serological tests for syphilis provide— a presumptive (but essential) 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 based on minor differences by genomic DNA sequencing.[51–53] A person with positive STS should be investigated and treated as for syphilis as a precautionary measure unless previous adequate treatment for syphilis is documented (1, D).

- Non-treponemal tests (NTT): using a complex antigen consisting of cardiolipin, lecithin and cholesterol (lipoidal tests, reagin tests) such as the Venereal Disease Research Laboratory test (VDRL), the Rapid Plasma Reagin test (RPR) and the Toluidine Red Unheated Serum Test (TRUST). All these tests detect a mixture of heterophile IgG and IgM and are manually performed, but they are cheap, simple and, if performed appropriately, have a relatively high sensitivity. NTT usually become positive approximately 10–15 days after the appearance 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.[22] Spontaneous seroreversion of NTT in patients with tertiary syphilis is hardly ever observed. Titres of NTT correlate grossly with disease activity and are used to monitor both disease activity and efficacy of treatment. Semi-automatized RPR tests have been developed.[54] However, these tests require further optimizations and subsequent evaluations.[55]
- Treponemal tests (TT): *T. pallidum* haemagglutination test (TPHA), *T. pallidum* particle agglutination test (TPPA), fluorescent treponemal antibody absorption test (FTA-abs test), treponemal enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), IgG or IgM 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 variation between individuals in interpretation but they are cheap and widely used all over Europe. EIA/ELISA and CLIA tests are most frequently automated but many of those remain expensive, suboptimally evaluated and/or standardized, and some may have suboptimal specificity.[22,56] TT mostly become positive in approximately 5–15 days after emergence of the chancre. Quantitation of TT is not useful in the diagnosis or management of syphilis (with possible exception of congenital syphilis). TT should therefore not be used to assess disease activity and treatment outcome and will remain positive for life in most patients.[22]
- Specific anti-*T. pallidum* IgM antibody tests: IgM-EIA, 19S-IgM-FTA-abs test and 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 the length of treatment. The usefulness of measuring IgM in the assessment of newborns and in neurosyphilis has not been appropriately validated.[22]

- Many rapid point-of-care tests (POCTs) using treponemal antigens have been developed in the last 25 years. Initially, tests had suboptimal sensitivity compared to traditional methods, but some of the latest assays have shown a substantial improvement.[47,50,57,58] These older tests also did not detect cardiolipin antibodies (i.e. patients with active infectious syphilis). New POCTs have substantially better performances for detection of both treponemal and non-treponemal antibodies.[59–64] Use of rapid POCTs 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 in the field or at peripheral clinics remote from laboratories (1, D). Currently, where appropriate laboratory diagnostics are available for syphilis in Europe, syphilis POCTs are not recommended for use. Nevertheless, they are useful for on-site testing of outreach populations and in antenatal settings where women with no confirmed syphilis tests during pregnancy can be tested before delivery.

Primary screening test(s)[4,22,47–49,64–68]

- TT [TPHA, MHA-TP, TPPA or EIA/ELISA/CLIA] – a TT-based screening algorithm, using by preference an automatized EIA/ELISA/CLIA, is used in many large, well-resourced European laboratories and is particularly suitable for automated high-throughput screening of asymptomatic populations including blood/plasma donors. The algorithm identifies persons with previous successful treatment of syphilis and those with untreated syphilis. It is usually more sensitive in detecting very early syphilis compared to the use of a screening NTT. However, it can also result in a high number of false-positive tests (i.e. very low positive predictive value) in low-prevalence populations.
- NTT [RPR or VDRL] – a NTT-based screening algorithm, preferably quantitative (i.e. to detect prozone phenomenon in infectious syphilis), is still recommended in some countries. In this algorithm, only active (infectious) syphilis is detected; however, it has a lower sensitivity compared to using a TT as primary screening test, and in particular, very early syphilis can be missed.
- TT combined with a NTT – this algorithm is particularly useful in cases where the suspicion of very early syphilis is high (recent chancre, contacts of syphilis cases etc.), because in some patients NTT may become reactive before TT.

Confirmatory test(s) if any screening test is positive[4,22,47–49,64–68]

- In the case, a TT being used alone as a primary screening test, if positive, a confirmatory TT of a different type is of limited value in informing treatment,[69,70] but a reflex quantitative NTT (reaching at least 1:8 to 1:16 dilution) should be performed in all cases on the same serum (1, B).

Although a confirmatory TT may be important for counselling, notification and may have a psychological impact, it has limited impact on treatment.[69] In patients with a positive TT, a negative NTT and no suspicion of very early syphilis (no chancre), both tests should be repeated after 1 month (1, D). However, CLIA and EIA used in many European settings have suboptimal specificity, resulting in a low positive predictive value in low-prevalence population.[22,49,56] If such tests are used, additionally a reflex confirmatory test by TPHA or TPPA should be performed (1, C).

- In the case a NTT alone is used as a primary screening test, a positive test must be followed by a reflex TT on the same serum. If quantitative NTT was not initially done, the NTT should be repeated quantitatively (1, B).
- In the case both a TT and a NTT are used as primary screening tests such as (EIA/ELISA/CLIA/TPHA/TPPA plus VDRL/RPR), the NTT must be performed quantitatively (if not initially done) in case of positive or discrepant screening tests (1, B).
- The IgG immunoblot for *Treponema 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 are widely used for monitoring the disease progression and effect of treatment at follow-up visits.
- A quantitative titre must be obtained on the very first day of treatment, that is, to provide a baseline for measuring subsequent changes in antibody titres (1, C).
- Serum should be obtained at 1 month, 3 months and every 6 months subsequently, ideally the same NTT should be used and the samples examined in the same laboratory. This should be continued until the NTT becomes negative or reaches a low plateau (1:1–1:4 sustained for 1 year in the absence of ongoing risk) (2, C). Patients with persistent high titres should remain under follow-up.

Laboratory: false-negative syphilis serology[4,22,37,38,43].

- All STS (TT and NTT) are negative before the appearance of a chancre and in the first about 5–15 days of the chancre. Both TT and NTT can be positive or negative or discordance can occur 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).[43] A negative NTT (or present at a low titre plateau, see above) along with a positive TT is frequently seen in treated and cured syphilis. Of note, particularly in late syphilis NTT can remain positive despite provision of adequate treatment.

- A persistent false-negative TT in the course of the disease is exceedingly rare and can usually be explained by technical problems in the laboratory testing or mix up of samples.
- A false-negative NTT (along with positive TT) may occur especially in early syphilis due to the prozone phenomenon (an excess of antibodies) when using undiluted serum. Dilution of serum for NTT must be performed in each case of a positive TT, at least to 1:8 or better 1:16.[71] This point may be of particular importance if the index/optical density units of EIA/ELISA/CLIA is high, and clinicians and laboratory personnel must ensure the NTT titration has been performed effectively (1, B).
- 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 and may not occur with modern tests.[72,73]
- Temporarily negative NTT and TT (reactive on subsequent testing) have occasionally been reported in secondary syphilis (so-called malignant syphilis). The diagnosis should then be supported by DFE, *T. pallidum* PCR, histology and/or histochemistry.
- Retesting with both TT and NTT is necessary on a second serum, when discordant results are found in an asymptomatic patient. In the case of chancre (in the absence of clinically overt vesicles), if DFE is positive or not available, treatment should be administered in all cases (syndromic approach) before obtaining laboratory results (*T. pallidum* PCR, *Herpes* PCR and STS). This recommendation is an important safeguard in many settings where follow-up is not optimal (2, C)

Laboratory: false-positive syphilis serology[4,22,37,38,74].

- 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 into acute (<6 months) and chronic (≥6 months). Acute BFP may be seen in postimmunization, recent myocardial infarction, many febrile infective illnesses (e.g. malaria, hepatitis, chickenpox and measles) and in pregnancy. Chronic BFP may be seen in injecting drug users, autoimmune diseases, HIV infection and chronic conditions such as leprosy, malignancies, chronic liver pathology and older age. The majority of BFP NTT sera show antibody titres of ≤1:4. A positive NTT must be retested on a second sample along with a TT.
- Occasional BFP TT tests (FTA-abs test more frequently than TPHA/MHA-TP/TPPA) may be seen in autoimmune diseases, Lyme disease and possibly during pregnancy. It can be excluded with, for example, the IgG immunoblot test for *T. pallidum*. All TT requiring visual reading of results (FTA-abs test, TPHA, TPPA...) are more subject to false-positive reactions at low titres of antibodies. Retesting on a second sample is necessary in case of negative NTT.

Laboratory tests to confirm or exclude neurosyphilis[15,24,75-87]. A complete clinical examination (neurological, ocular and otologic) is recommended in every patient with positive STS. However, in those without symptoms it is rarely contributory.[79,81,83,86-88]

- 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 (whether the patient is HIV positive or negative), unless there are neurological, ocular or auricular symptoms (1, A).
- CSF assessment is indicated in patients with:
  - clinical evidence of neurological, ocular and auricular involvement, whatever the stage of the disease[79] (1, C)
  - tertiary syphilis (cardiovascular, gummatous) (1, D)
- The 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 CSF penicillin levels after injection of benzathine penicillin G (BPG) are frequently under the reputed penicillin treponemicidal level,[89] progression from asymptomatic to symptomatic neurosyphilis is extraordinarily rare (even in HIV-positive patients).[86] As CSF assessment is not without its own dangers, LP is not recommended in the vast majority of asymptomatic patients (1, D).
- Although robust evidence is lacking, some experts still recommend CSF assessment in asymptomatic patients in the following situations for exclusion of asymptomatic neurosyphilis (2, D):
  - in HIV-positive patients with late syphilis AND CD4 cells ≤ 350/mm^3 AND/OR a serum VDRL/RPR titre >1:32[87]
  - in those who have serological failure (<fourfold decrease in the antibody titre of a NTT 6–12 months after treatment of early syphilis) or are serofast (persistence of low antibody titre, i.e. ≤4, of a NTT, 1–2 years after treatment of early syphilis).
  - in those given alternative treatment (e.g. tetracyclines such as doxycycline) for late syphilis
- Examination of CSF: must include total protein, number of mononuclear cells, a TT (TPHA/MHA-TP/TPPA) and a NTT (preferably VDRL and otherwise RPR).[82]
  - A 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).[75,76,87] 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 1:3rd of cases of neurosyphilis but a positive test can in the absence of substantial blood contamination be considered as indicative of neurosyphilis in late disease. However, in early syphilis the significance of a positive CSF VDRL test is less clear.[83]
- A positive CSF TT (TPHA/TPPA) does not confirm the diagnosis of neurosyphilis but a negative CSF TT means neurosyphilis is highly unlikely.[15,84,85]
- Several indices can be calculated to evaluate the significance of CSF anti-treponemal immunoglobulins, taking into account transfer through the blood–brain barrier. However, none of these have proven to be of significant practical use.[4]

- PCR assays for detection of *T. pallidum* in CSF to help establish a diagnosis of neurosyphilis are currently considered of limited value since they have shown low sensitivity and suboptimal specificity.[15,24,90]
- In case of an abnormal CSF examination (high protein level and/or hypercytosis), repeat CSF control 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 and in patients with latent syphilis of unknown duration. A chest X-ray is rarely contributory.[91]

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 signs are found.
- Performing CSF examination is controversial as intravenous (IV) penicillin therapy will be initiated anyway. It may be helpful to exclude other pathologies in the differential diagnosis and if found to be abnormal in someone with neurosyphilis, appropriate follow-up is required to ensure all markers return to acceptable levels (2, C).

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 and should have a full STI assessment. All patients with syphilis should also be tested for HIV and HCV if risk factors (as assessed by local epidemiology) are present. Assessment and vaccination for hepatitis B should also be considered if appropriate.

General remarks[87,92–97]

- A treponemicidal level of antimicrobial should be achieved in the serum and in the case of neurosyphilis also strived for as much as feasible 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* concentration (0.36 mg/L).
- The duration to maintain a treponemicidal level of antimicrobials should be at least 7–10 days to cover a number of bacterial generation 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 (2, D). Treponemes have been shown to persist despite apparently successful treatment.[93] 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 concentration in blood for up to 21 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 BPG and other penicillins.
- 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.[97,98]
- Non-penicillin antibiotics have been evaluated. These include tetracyclines (doxycycline is the preferred tetracycline with good penetration into the CSF) and macrolides, taken orally.[99–103] Doxycycline has been evaluated more than any other non-penicillin antibiotics but all studies have been observational and retrospective.[100–103] Newer anti-treponemal antibiotics include the intramuscular or intravenous extended-spectrum cephalosporin (ESC) ceftriaxone.[103–106] Ceftriaxone has good CSF penetration, but it requires multiple injections, the dose and duration are not standardized and it does not offer any advantages over single-dose BPG.[107] 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 a dangerous option although cross-allergies are not frequent.

History of penicillin anaphylaxis is an absolute contraindication.[65] The oral ESC cefixime is currently evaluated for treatment, but appropriate data are still pending.

- Azithromycin has shown good treponemicidal activity in animal studies and several controlled studies, mostly in Africa. However, rapid emergence of resistance to azithromycin and clinical failures have been described in several studies.[33,108–113]
- The host immune response is important as 60% of untreated patients will not develop clinical features other then primary lesions.[114] CSF involvement is common in early syphilis.[76,90] Although both parenteral BPG and standard regimens of parenteral procaine penicillin do not achieve treponemicidal CSF levels,[77,84] the prevalence of late syphilis, including neurosyphilis, remains low, indicating that treatment at current doses 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 the diluent by the same volume of 1% lidocaine solution may reduce the pain associated with injection[115] and in late syphilis may improve compliance with the second and third injection. Compliance with daily intramuscular injections with procaine penicillin has been shown to be good in the United Kingdom.[116] The control of syphilis over the past 50 years has been excellent compared to the prepenicillin era and 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 the 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 (2, D). HIV coinfection does not appear to increase the risk of developing a more aggressive course of early syphilis. Modest differences have been published with a slightly higher prevalence of (1) multiple chancres and (2) concomitant chancre and secondary eruption in patients infected with HIV. The risk of ocular and neurological involvement is not increased in HIV-positive patients with early syphilis. Thus CSF assessment in early syphilis is indicated only in patients with overt ocular, auricular or neurologic symptoms (for the same reason as in non-HIV-infected patients) (1, A)[4,65,66]

Recommended treatment regimens (Table 1)

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

First-line therapy option[2,4,66,90,117]

- BPG 2.4 million units intramuscularly (IM), given as one injection of 2.4 million units or two separate injections of 1.2 million units in each buttock, on day 1 (1, B)

Replacing part (i.e. 0.5–1 cc) of the diluent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection,[118] although this is not feasible in case of premounted BPG syringes.

Patients should be kept for 30 min for clinical review after injection.

Although there are more than ten different pharmaceutic companies manufacturing BPG in Europe, shortages and supply disruptions are common.[119]

Second-line therapy option

- Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available (1, C)

Bleeding disorders

- Ceftriaxone 1g intravenously (IV) in a single daily dose for 10 days (1, C)
- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days (1, C)

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 (1, C)
- Desensitization to penicillin is an option but not possible in many settings and labour intensive.

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

First-line therapy option

- BPG 2.4 million units IM, given as one injection of 2.4 million units or two separate injections of 1.2 million units in each buttock, on day 1, 8 and 15 (1, C)

Replacing part (i.e. 0.5–1 cc) of the diluent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection,[118] although this is not feasible in case of premounted BPG syringes.

Patients should be kept for 30 min for clinical review after injection.

Second-line therapy option

- Procaine penicillin 600 000 units IM daily for 17–21 days, i.e. if BPG is not available (1, C)

Penicillin allergy or parenteral treatment refused Some specialists recommend penicillin desensitization because the evidence base for the effectiveness of non-penicillin regimens is weak.

- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 21–28 days (2, D)

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 also achieve treponemicidal levels in the CSF, i.e. the procaine penicillin/probenecid combination (IM) and ceftriaxone (IV or IM). The availability of probenecid may 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 for 10–14 days (1, C)

Second-line therapy option If hospitalization and IV benzyl penicillin is impossible.

- Ceftriaxone 1–2 g IV in a single daily dose for 10–14 days (1, C)
- Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both for 10–14 days (1, C)

Penicillin allergy

- Desensitization to penicillin (in fact, induction of tolerance) followed by the first-line regimen (1, C)

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.[120–122]

Women with persistently negative NTT results are very unlikely to transmit syphilis during pregnancy.[123] In case of a positive TT along with a negative NTT, repeat NTT after one month to eliminate a very early syphilis. Most transmissions to the fetus occur in late pregnancy (after 28 weeks) and treatment before this period will usually prevent congenital features.[120]

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

- BPG 2.4 million units IM single dose (or 1.2 million units in each buttock) (1, B)

Note: some specialists recommend 2 doses of BPG 2.4 million units (days 1 and 8) but the evidence to support this recommendation is limited.[123]

Patients should be observed for adverse reactions to penicillin for 30 min after injection.

Second-line therapy option

- Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available (1, C).

Penicillin allergy

- Desensitization to penicillin followed by the first-line regimen (1, C)

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

- All pregnant women should be screened at their first antenatal visit (first trimester) (1, C). Serology should be repeated, ideally during third trimester at 28–32 weeks' gestation and at delivery, in cases where there is increased risk and in settings with a high syphilis prevalence (1, C). Furthermore, for pregnant women with no documented previous test, testing should be performed at delivery.

Congenital syphilis

Confirmed congenital infection[120,121,123–125]

- Congenital syphilis is confirmed by identifying *T. pallidum* by DFE or PCR in the placenta or autopsy material, exudate from suspicious lesions or body fluids, e.g. nasal discharge.

Presumed congenital infection A presumptive diagnosis of congenital syphilis is made in:

- A stillborn neonate with a positive TT for syphilis.
- Children with a positive TT for syphilis in combination with one or more 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 RPR/VDRL 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 RPR/VDRL in the child 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.
- A child >12 months of age with a positive TT for syphilis and in whom sexual abuse has been excluded.

Late congenital syphilis Late congenital syphilis is diagnosed based on:

- Clinical features: interstitial keratitis, Clutton's joints, Hutchinson's incisors, mulberry molars, high palatal arch, perioral rhagades, deafness, frontal bossing, short maxilla,

protuberance of mandible, saddle nose deformity, sternoclavicular thickening, paroxysmal cold haemoglobinuria, neurological or gummatous involvement.
- Serological tests: these can initially be negative in infants infected in late pregnancy and should be repeated. When the mother is treated during the last trimester of pregnancy, the treatment can be inadequate for the child and the child may still develop congenital syphilis.

Investigations
- RPR/VDRL (quantitative), 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, since 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) for 10–14 days (1, D)

Second-line therapy option (only if CSF is normal)
- BPG 50 000 units/kg IM (single dose) up to the adult dose of 2.4 million units (1, D) or procaine penicillin 50 000 units/kg IM daily for 10–14 days, i.e. if BPG is not available (1, D)

HIV-infected patients

General remarks[87,90,126–134]
- 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 anecdotally.
- In HIV-infected individuals with clinical suspicion of syphilis and negative syphilis serology (confirmed when repeated), it is advisable to perform other diagnostic tests, e.g. histological, immunofluorescent or PCR examination of a biopsy from a clinically suspected lesion or DFE or PCR to identify treponemes in the exudate from early syphilitic lesions.[65]
- 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.

Treatment of syphilis in patients with concomitant HIV infection
- Treatment should be given as for non-HIV-infected patients with careful follow-up to ensure an appropriate response.

Syphilis induced by solid organ transplant

First-line therapy options
- BPG 2.4 million units IM (one injection 2.4 million units single dose or 1.2 million units in each buttock) weekly on days 1, 8 and 15 (1, B)[10,135]

Second-line therapy option
- Procaine penicillin 600 000 units IM daily for 10–14 days, i.e. if BPG is not available (1, C)[135]

Penicillin allergy Some specialists recommend penicillin desensitization because the evidence base for the effectiveness 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 (1, C)[135]

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 rigours, resolving within 24 h.
- Common in early syphilis (10–25%)[136] 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.
- May be more frequent with penicillin than with doxycycline.[136]
- Uncommon in late syphilis but can potentially be life-threatening if involvement of strategic sites (e.g. coronary ostia, larynx, nervous system).[137,138]
- Prednisolone can prevent the febrile episode.[139] Although unproven, biological plausibility suggests that steroids may help to prevent severe deterioration in optic neuritis and uveitis following a reaction to treatment in early syphilis.
- 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 syphilis treatment 24 h after commencing prednisolone (2, D)
- Antipyretics

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

- Due to inadvertent IV injection of procaine penicillin, the risk of which may be minimised by the 'aspiration technique' of injection.
- Characterized by fear of impending death and 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 a common cause.
- Management:
  - Epinephrine (adrenaline) 1:1000 (1 mg/mL) IM 0.5 mL followed by:
    - injectable antihistamine, e.g. chlorpheniramine 10 mg IM/IV or clemastine 2–4 mg IM/IV
    - hydrocortisone 100 mg IM/IV

Pre-exposure prophylaxis and syphilis

Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate–emtricitabine is effective for reducing HIV acquisition but may – at the individual level – result in an increase in the frequency of condomless sex and several studies have shown it could increase the acquisition of STIs in general.[140,141]

This PrEP population should be tested for syphilis every 3 months. A few studies have evaluated pre-exposure (or immediate post-exposure) prophylactic treatment of STIs using doxycycline, taken continuously[142] or intermittently.[143] Although this has been shown to potentially decrease the incidence of syphilis and chlamydia, follow-up has been short and there is a risk of promoting development or acquisition of tetracycline resistance in STI bacteria and the microbiome more generally. Additional studies in different settings and with longer follow-up are required before this prophylactic treatment can be recommended.[144]

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] or by a health department: provider referral), health education and confirmation of any past treatment history. Further advice from International Union against STI (IUSTI) on this matter can be found in the IUSTI guideline on Partner management at https://iusti.org/treatment-guidelines/.
- Clear information about syphilis should be given to all infected individuals and their sexual contacts. Patient information resources can be found at https://iusti.org/patient-information/.
- Although the division of latent syphilis in early and late stages is useful for determining 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 classified as late latent) can be due to early, infectious, latent syphilis.
- Sexual contact notification helps to reduce the disease burden in the community, identify asymptomatic syphilitic patients and can delineate relevant sexual risk networks. The use of Internet-based notification systems and community outreach programmes may assist in identifying and engaging with sexual partners.
- Sexual contacts should include all those individuals who have had oral, genital 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.[145] Partner notification may have to be extended to 2 years for patients with secondary syphilis associated with clinical relapse or in early latent syphilis. Longer time periods may be required in those with late latent and tertiary syphilis.[144]
- 46–60% of traced sexual contacts, including pregnant women, of patients with early syphilis are likely to be infected.[146]
- 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, 6 weeks and 3–6 months).
- Serological tests for syphilis should be performed at the first visit and repeated at 6 weeks and 3–6 months.
- Notification of syphilis to the relevant national authority is mandatory in most European countries, particularly early syphilis and congenital syphilis. The ECDC is responsible for the EU/EEA-wide surveillance of communicable diseases including syphilis.

Follow-up and test of cure

The follow-up of treated syphilis patients to ensure cure and detect reinfection or relapse is achieved by assessing the clinical and serological response to treatment. Globally, many studies have confirmed that follow-up is suboptimal.[126,147]

- Early syphilis, minimum clinical and serological (VDRL/RPR) follow-up at 1 month, 3 months then at 6 and 12 months.
  - After treatment of early syphilis, the titre of a NTT taken at day 0 (e.g. VDRL and/or RPR) should decline by ≥2 dilution steps (≥fourfold decrease in titre of antibodies) within

6 months.[1,4,22] However, around 15% of 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.[148–150] These patients should be tested again at 12 months. Patients with repeat early syphilis have usually higher titres and a slower decline in titres post-treatment.[101,151,152]

- If a fourfold decrease in the antibody titre of a NTT does not occur after 6–12 months, ('serological failure') some professionals recommend additional treatment with one weekly injection of BPG 2.4 million units for 3 weeks but no robust evidence for this recommendation exists (2, D)
- A negative NTT can be obtained in a substantial number of (but not in all) patients treated for early syphilis after 1–2 years. Patients with repeat syphilis serorevert less often. A negative NTT after treatment is considered to be the best confirmation of cure. In patients with persistent low titres (i.e. ≤4), in NTT (named the serofast state) strict follow-up is recommended but in the absence of ongoing risk these patients should be considered as successfully treated. In patients with persistent high titres of NTT (i.e. ≥8), CSF assessment should be considered with the aim of detecting asymptomatic neurosyphilis, although there is no robust evidence for this recommendation (2, D)
- A TT may remain positive for life even following effective treatment; and appropriate 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 a low titre range, follow-up after treatment is generally not indicated (2, D).
- An increase of ≥2 dilution steps (fourfold increase in antibody titre) in a NTT, in the absence of clinical symptoms, suggests reinfection or hypothetic relapse. Treatment should be given according to the above guidelines for latent syphilis (early if <1 year; late if ≥1 year) (1, C) Patients at high risk of reinfection should be checked frequently using NTT, e.g. every 3 months. (2, C). Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.
- Follow-up examination of CSF should be performed 6 weeks to 6 months after treatment of neurosyphilis to monitor decrease of white blood cells and proteins.[153] (2, D) Limited data suggest that CSF control could be avoided in patients with normalization of serum RPR titres.[154]

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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Current composition of the European Guideline Editorial Board can be found at https://iusti.org/treatment-guidelines/

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Search Strategy and Grading Levels of Evidence

Appendix 1.

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Appendix 1

Search strategy

This guideline has been updated from the IUSTI-Europe Syphilis guideline 2014.[4] Evidence for this guideline was provided by review of the Medline/PubMed, Embase and Cochrane Library from 2014 to October 2019, using the term syphilis, neurosyphilis, congenital syphilis and *Treponema pallidum*.

The levels of evidence and grading of recommendations

Levels of evidence

All key recommendations made for diagnosis and management have been graded for the level of evidence.

A Grade 1 recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording: 'We recommend …' or 'It is recommended …'

A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording: 'We suggest...' or 'It is suggested...' The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences, and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and is defined as follows:

- Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs) or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.
- Grade B evidence means moderate-quality evidence from randomized trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.
- Grade C evidence is low-quality evidence from controlled trials with several serious limitations or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
- Grade D evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.