2020 European Guideline on the Management of Syphilis

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Conflicts of interest  
The authors have no conflicts of interest related to this guideline.

Funding sources  
None.

Abstract  
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 high risk populations

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. 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. 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). This guideline is an update of the 2014 European guideline on the management of syphilis.

**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; 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)/sexually transmitted infection (STI) clinics afterwards referred to as “sexual health clinics”

**DIAGNOSIS**

**A. Clinical**

Definition of stages is clinical, chronology begins with the onset of 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.\textsuperscript{10}

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

Primary syphilis: a chancre, usually with regional lymphadenopathy. The chancre 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. Chancre often atypical in appearance and may be multiple, painful, deep and indistinguishable from herpes.\textsuperscript{11-13} Any anogenital ulcer should be considered syphilitic unless proven otherwise. Chancre 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\textsuperscript{14-19} 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, generalised lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis, aortitis and glomerulonephritis are possible. Meningitis, cranial nerve palsy, auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papillary edema), 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)\textsuperscript{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 OR unequivocal evidence that the disease was acquired in the past year (on the basis of clinical signs in patient and partners).\textsuperscript{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

**B. Laboratory**

**Demonstration of *T. pallidum***

- Direct detection methods provide definitive diagnosis of syphilis.
- Darkfield examination (DFE) of chancres and erosive cutaneous lesions is the old gold standard method for definitive diagnosis and gives immediate results. However, the method is labor intensive, subjective, and might provide both some false positive and (many) false negative results.\(^{21,22}\)
- Polymerase chain reaction (PCR) tests, preferred method particularly but not exclusively 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.\(^{22-28}\) 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.\(^{27,28}\) Not for routine diagnosis.
- Hybridization in tissues\(^29\) Not for routine diagnosis
- Warthin-Starry (argent) staining on tissues is very difficult to perform and of limited value in most cases.
- (Direct fluorescent antibody test is obsolete)
- For molecular epidemiological typing, PCR, PCR-restriction fragment length polymorphism (RFLP) and/or DNA-sequencing (e.g. multilocus sequence typing (MLST) or 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)** \(^{22,37-50}\)

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 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 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 and are manually performed, but they are cheap, simple and, if appropriately performed, have a relatively high sensitivity. NTT most frequently become positive approximately 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 1-2 years following infection and remains positive with low titres in very late disease. Spontaneous seroreversion of NTT along with tertiary syphilis is hardly ever observed. Titres of NTT grossly correlate with disease activity and are used to monitor both disease activity and efficacy of treatment. Semi-automatized RPR tests have been developed. However, these tests require further optimizations and subsequent evaluations.

- Treponemal tests (TT): T. pallidum Haemagglutination test (TPHA), T. pallidum Passive 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 individual variations in interpretation but they are cheap and widely used all over Europe. EIA/ELISA and CLIA-tests are most frequently automatized but many of these remain expensive suboptimally evaluated and/or standardized, and some may have suboptimal specificity. TT mostly become positive in approximately 5-15 days after emergence of the chancre. Note: results of EIA/ELISA/CLIA are given in indexes/optical densities, which are different from quantitative titration by serum dilution; they only reflect approximately the quantity of antibodies in one serum. Quantitation of TT is not useful 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.

- 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 main usefulness is in the assessment of newborns and CSF.
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 substantially improved sensitivity.\cite{47,50,57,58} However, these older tests 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.\cite{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 at field level or peripheral clinics remote from laboratories. Currently, where appropriate laboratory diagnostics is 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 delivery clinics where women with no confirmed syphilis tests during pregnancy can be tested before delivery.

**Primary screening test(s)**\cite{4,22,47-49,64-68}

- A TT [TPHA, MHA-TP, TPPA or EIA/ELISA/CLIA]. This screening algorithm, using by preference an automatized EIA/ELISA/CLIA, 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 more sensitive 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 (very 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 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 particularly very early syphilis can be missed.

- 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**\cite{4,22,47-49,64-68}

- In the case a TT alone is used as a primary screening test, if positive, a confirmatory TT of a different type is of limited value in informing treatment \cite{69,70} but a reflex quantitative NTT (reaching at least 1:8 to 1:16 dilution) must be performed in all cases on the same serum. Although it still may be important for counselling, notification and may have a psychological impact, it has limited impact on treatment.\cite{69} Patients with positive TT and
persistent (test repeated after 1 month) negative NTT should not be treated unless there is suspicion of very early syphilis. However, CLIA and EIA used in many European settings have suboptimal specificity, resulting in a low positive predictive value in low prevalence populations. If such tests are used, a reflex confirmatory test by TPHA or TPPA should be performed.

- 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.
- In the case both TT and NTT are used as primary screening tests such as (EIA/ELISA/CLIA/TPHA/TPPA plus VDRL/RPR), NTT must be performed quantitatively if not initially done (particularly if TT is positive).
- IgG-immunoblot for *Treponema pallidum* has no added major value to other TT. It is expensive and interpretation of undetermined immunoblot is elusive (1 to 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.
- 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 month, 3 months and every 6 months subsequently, ideally the identical NTT should be used and the samples examined in the same laboratory. This should be continued until the NTT becomes negative or attains a low plateau (1:1-1:4 sustained for 1 year in the absence of ongoing risk) (IV C). Patients with higher titres should remain under follow up.

**B1. Laboratory: false negative syphilis serology**

- All STS (TT and NTT) are negative before the appearance of a chancre and in the first 5-15 days of the chancre. Both TT and NTT can be positive or negative or 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. Note: particularly in late syphilis NTT can remain positive despite provision of adequate treatment.
- A 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 (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\textsuperscript{71} This point may be of particular importance if the index/optical density units of EIA/ELISA/CLIA is high, clinicians and laboratory specialists must ensure the NTT titration has been effective.

• 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 be recorded with modern tests\textsuperscript{72,73}.

• Temporarily negative NTT and TT (reactive on subsequent testing) have occasionally been reported in secondary syphilis (so-called malignant syphilis). Diagnosis should then be supported by DFE, \textit{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 (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 (\textit{T. pallidum} PCR, \textit{Herpes} PCR, and STS). This recommendation is an important safeguard in many settings where follow up is not optimal.

\textbf{B2. Laboratory: false positive syphilis serology} \textsuperscript{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 as acute (<6 months) and chronic (>6 months). Acute BFP may be seen in postimmunisation, recent myocardial infarction, many febrile infective illnesses (e.g. malaria, hepatitis, chicken pox, measles, etc.), and 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 old age. The majority of BFP NTT sera show antibody titres of \(\leq 1:4\). A positive NTT must be retested on a subsequent serum along with a TT.

• Occasional BFP TT tests (FTA-abs test more than TPHA/MHA-TP/TPPA) may be seen in autoimmune diseases, Lyme disease and possibly during pregnancy and can be excluded with, for example, the IgG immunoblot test for \textit{T. pallidum}. All TT with visual reading of results (FTA-abs test, TPHA, TPPA...) can be more 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\textsuperscript{15,24, 75-87.}

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\textsuperscript{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 (HIV positive or negative), 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\textsuperscript{79}
  - 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 (even in HIV-positive patients)\textsuperscript{86} As CSF assessment is not without its own dangers, LP investigation is not recommended in the vast majority of asymptomatic patients.
- Although robust evidence is lacking, some experts still recommend CSF assessment 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 $>1:32$\textsuperscript{87}
  - in case of serological failure or serofasting
  - 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 VDRL and otherwise RPR))\textsuperscript{82}
  - 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).\textsuperscript{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 1:3 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.\textsuperscript{83}
- A positive CSF TT (TPHA/TPPA) does not confirm the diagnosis of neurosyphilis but a negative CSF TT result is highly unlikely in neurosyphilis\textsuperscript{15,84,85}
- Several indexes taking into account blood-brain barrier and aiming at evaluation of intrathecal synthesis of immunoglobulins have been produced with none being of real practical use.\textsuperscript{4}
  - PCR assays for detection of \textit{T. pallidum} in CSF to help establish a diagnosis of neurosyphilis are currently considered of little value since tests to date have shown low sensitivity and suboptimal specificity.\textsuperscript{15,24,89}
  - 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).

C. 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.\textsuperscript{90}

D. 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 intravenous (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, appropriate follow-up is required to ensure all markers return to acceptable levels.

E. 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.

**A. General remarks** 87,91-96

- 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).
- Duration of 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. Treponemes have been shown to persist despite apparently successful treatment.92 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 21-28 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.96,97
- 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.98, Doxycycline has been more evaluated than any other non penicillin antibiotics but all studies have been observational and retrospective.99-102 Erythromycin is less effective and does not penetrate the blood-brain or placental barrier well. Newer anti-treponemal antibiotics include
intramuscular or intravenous extended-spectrum cephalosporin (ESC) ceftriaxone.\textsuperscript{102-105} 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.\textsuperscript{106} 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.\textsuperscript{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.\textsuperscript{33,107-112}

- The host immune response is important as 60\% of untreated patients will not develop clinical features other than primary lesions.\textsuperscript{113} CSF involvement is common in early syphilis.\textsuperscript{76,89} Although both parenteral BPG and standard regimens of parenteral procaine penicillin do not achieve treponemicidal CSF levels,\textsuperscript{77,84} 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\% lidocain solution may reduce the pain associated with injection\textsuperscript{114} and in late syphilis may improve compliance of the second and third injection. Compliance with daily intramuscular injections with procaine penicillin has been shown to be good in the United Kingdom.\textsuperscript{115} 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 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 \( \leq 350/\text{mm}^3 \) 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. Modest differences have been published with a slightly higher prevalence of 1) multiple chancre, and 2) concomitant chancre and secondary eruption in patients infected with HIV. 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
B. Recommended treatment regimens

B1. 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] (1,B) |
  | Replacing part (i.e. 0.5 to 1cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection. |
  | This is not feasible in case of pre-mounted BPG syringes. |
  | Patients should be kept for 30 min clinical review after injection. |
  | Although there are more than ten different pharmaceutic companies manufacturing BPG in Europe, shortages and supply disruptions are regular. |

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

Bleeding disorders:
- Ceftriaxone 1g intravenously (IV) daily for 10 days
  
  | [III; B] (1,C) |
- Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days
  
  | [III; B] (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
  
  | [III; B] (1,C) |
- Desensitization to penicillin is an option but not possible in many settings and labor consuming.
B2. 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 [III; B] (1,C)
  Replacing part (i.e. 0.5 to 1cc) of the solvent by lidocaine 1% solution without epinephrine may reduce the discomfort associated with injection. This is not possible in case of pre-mounted syringes.
  Patients should be kept for 30 min clinical review 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] (1,C)

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] (1,C)

B3. 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 (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 hours for 10-14 day [III; B] (1,C)

Second line therapy option:
If hospitalization and IV benzyl penicillin is impossible
• Ceftriaxone 1-2 g IV daily for 10-14 days [III; B] (1,C)
• Procaine penicillin 1.2-2.4 million units IM daily AND probenecid 500 mg four times daily, both for 10-14 days [IIb; B] (1,C)

Penicillin allergy:
• Desensitization to penicillin (in fact, induction of tolerance) followed by the first line regimen [III; B] (1,C)

C. Special considerations

C1. Pregnancy
In pregnant women with untreated early syphilis, 70-100% of infants will be infected, with stillbirths in up to one-third of cases.\textsuperscript{119-121} Women with persistently negative NTT results are very unlikely to transmit syphilis during pregnancy.\textsuperscript{121} 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\textsuperscript{119}.

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) [I; B] (1,B)
  Note: some specialists recommend 2 doses of BPG 2.4 million units (day 1 and 8) but the evidence to support this recommendation is limited.\textsuperscript{123} 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] (1,C)

Prevention of congenital syphilis by serological screening during pregnancy and preventive neonatal treatment:
• All pregnant women should be screened at first antenatal visit (first trimester). Serology should be repeated, ideally during third trimester at 28-32 weeks’ gestation and at delivery, in case of increased risk and in settings with high syphilis prevalence. Furthermore, for pregnant women with no documented previous test, testing should be performed at delivery.
• 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.
**C2. Congenital syphilis** 119,120,122-124

**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 TT for syphilis.
- Children with a positive TT 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 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 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 TT 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, perioral 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.

**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 (since false-positive and -negative tests may result).

- Blood: Full blood count, liver function, electrolytes
- CSF: cells, protein, RPR/VDRL, TPHA/TPPA
- X-rays long bones
- Ophthalmic assessment as indicated

**First line therapy option:**
- Benzyl penicillin 150,000 units/kg IV daily (administered in six doses every 4 h) during 10-14 days \([IV; C] (1,D)\)
- 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 \([IV; C] (1,D)\)
  - b. Second line therapy: Procaine penicillin 50,000 units/kg IM daily for 10-14 days, i.e. if BPG is not available \([IV; C] (1,D)\)

**C3. HIV infected patients**

**General remarks** \(87,89,125-133\)
- 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 annecdotally.
- 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 \(65\).
- 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, however, some specialists recommend CSF assessment 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.
  Note: Careful follow-up is essential.

C4. 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 day 1, 8 and 15 [III; B] (1,C) \[10,134\]

Second line therapy option:
• Procaine penicillin 600,000 units IM daily for 10-14 days, i.e. if BPG is not available [IIb; B] (1,C)\[134\]

Penicillin allergy:
• Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally during 21-28 days\[134\]

C5. Reactions to treatment

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

Jarisch-Herxheimer reaction:
• An acute febrile illness with headache, myalgia, chills and rigors, resolving within 24 hours.
• Common in early syphilis (10-25%)\[135\] 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\[135\]
• Uncommon in late syphilis but can potentially be life threatening if involvement of strategic sites (e.g. coronary ostia, larynx, nervous system)\[136,137\]
• Prednisolone can prevent the febrile episode.\[138\] Although steroids are unproven at ameliorating local infection, biological plausibility suggests that steroids 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 syphilis treatment after 24 h of commencing prednisolone [IV; C] (1,D)
- Antipyratics

**Procaine reaction (procaine psychosis, procaine mania, Hoigné syndrome):**
- Due to inadvertent IV injection of procaine penicillin and may be minimised by the "aspiration technique" of injection.
- Characterised by fear of impending death, may cause hallucinations or fits immediately after injection. Lasts less than 20 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:
    - Antihistamine e.g. chlorpheniramine 10 mg IM/IV
    - Hydrocortisone 100 mg IM/IV

**C6. Pre-exposure prophylactic syphilis treatment**

Pre-exposure prophylaxis with tenofovir disoproxil fumarate-emtricitabine is efficient for reducing HIV acquisition but may result in high risk sexual behaviour and several studies have shown it could increase the acquisition of STIs in general ^139,140^ 

This population should be tested for syphilis every 3 months. A few studies have evaluated a pre-exposure (or immediate post-exposure) prophylactic treatment of STIs by doxycycline, taken continuously^141^ or intermittently. ^142^ Although it has been shown to potentially decrease the incidence of syphilis and chlamydia slightly, follow-up has been short and the risk of promoting development or acquisition of tetracycline resistance in the aetiological agent of STIs and the microbiome more generally. Additional studies in different settings and with longer follow-up are required before this prophylactic treatment can be broadly recommended. ^143^

**D. 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 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

• Although the division of latent syphilis in early and late stages has been useful for treatment and partner notification, this classification can be problematic for use in surveillance, as a substantial number of late, hypothetically non-infectious, latent syphilis cases (latent syphilis of unknown duration was classified as late latent) may be due to probable early, infectious, latent syphilis.

• 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 partners 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, 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. Partner notification may have to extend 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 tertiary 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 national 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.
E. Follow-up and test of cure

The follow-up of treated syphilis patients to ascertain 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.125,146

- Early syphilis, minimum clinical and serological (VDRL/RPR) at 1 month, 3 months then at 6 and 12 months.
  - After treatment of early syphilis the titer 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 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 unknown147-149 These patients should be tested again at 12 months. Patients with repeat early syphilis have usually higher titres and slower decline in titres100,150,151
  - 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 [IV; C]. (2,D)
  - A negative NTT can be obtained in a substantial number (but not in all) of patients treated for early syphilis after 1 to 2 years. Patients with repeat syphilis serorevert less often. A negative NTT after treatment is considered as the best test 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 can be considered in the aim of detecting asymptomatic neurosyphilis, although there is no robust evidence for this recommendation [IV; C] (2,D)
  - 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 titer range, follow-up after treatment is generally not indicated.
- An increase of ≥2 dilution steps (fourfold increase in antibody titre) in a NTT, in the absence of clinical symptoms, suggests reinfection or relapse. Treatment should be given according to the above guidelines for latent syphilis (early if ≤1 year; late if >1 year). Patients at high risk of reinfection should be checked frequently using NTT, i.e. every 3 months. 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.\textsuperscript{152}

\textbf{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.

\textbf{Scope}

This guideline has been written in order to assist health care professionals to diagnose and treat and follow-up patients with syphilis. The paper was updated with new information available in the fields of diagnostic and treatment. The use of these guideline in clinical routine should improve patients care.

\textbf{Target population}

The guideline is addressed to health care professionals involved in the management of patients with syphilis. The general guideline recommendations are easy to understand and can be also used by the patients.

\textbf{Search strategies and level of evidence grading}

Appendix I.

\textbf{Acknowledgements}

We are grateful for valuable input on the present guideline to Olga DOLYA (if ever)

\textbf{Composition of the European Guideline Editorial Board}

Current composition can be found at: https://www.iusti.org/regions/Europe/euroguidelines.htm

\textbf{List of contributing organisations}

Current list can be reviewed at: http://www.iusti.org/regions/Europe/
The present guideline was reviewed and approved by representatives from the EDF, UEMS-EBDV, EADV, ECDC, WHO European Regional Office, and ESCMID. List of contributing organizations and membership can be reviewed at http://www.iusti.org/regions/Europe/euroguuidelines.htm.

**Proposed review date: 2025**

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**Search strategy**
This guideline has been updated from the IUSTI-Europe Syphilis guideline 2014. 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*.

**Tables of level of evidence and grading of recommendation**

**Levels of Evidence:**

**Statement on declarations of interest**
The authors have no conflicts of interest related to this guideline.