

# Syphilis: A Review of the Diagnosis and Treatment

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**Abstract:** Syphilis has re-emerged as an important cause of morbidity, mortality and a possible transmission factor in the spread of HIV infection. The control of syphilis requires early identification and treatment of cases. Here the diagnostic tests are reviewed and discussed, including when to think of lumbar puncture for the examination of neurosyphilis. The British, European and American guidelines for treatment at each stage are compared; with efficacy and side effect profile of regimens considered and advice on management of complications. Stemming the spread of infection requires increased education, early diagnosis and prompt notification of partners.

## INTRODUCTION

The worldwide re-emergence of syphilis brought this complex sexual infection back to mainstream medicine. Since the late 1990s there has been a well documented resurgence of infectious syphilis beginning in Europe, predominately among men who have sex with men (MSM) [1-6]. Syphilis has a myriad of presentations and can mimic many other infections and immune-mediated diseases. The complex and variable manifestations of the disease mean that vigilance is required in every medical discipline. Reports of local outbreaks have made reference to the diagnostic difficulties in order to remind clinicians to think of syphilis when encountering such patients [1-6]. The control of syphilis requires early identification and treatment of cases. This calls for tests that are easily administered and interpreted, and treatment that is fast, efficacious and side effect free. Stemming the spread of infection will also require increased education and prompt notification of partners.

## STAGING DISEASE

Syphilis infection is characterized by different phases of disease and these can be initially divided into early and late stages (Fig. 1). These reflect the infectious period, thus early syphilis is infectious and at late stage the infection is not transmittable. Early syphilis can be divided again into primary, secondary and early latent syphilis depending on clinical presentation [7]. Primary syphilis is characterized by the chancre that occurs at the site of inoculation: classically nontender, indurated and nonpurulent ulcer. Secondary syphilis is most often heralding by a maculopapular rash involving palms and soles but this stage can include laryngitis, condylomata lata, hepatitis, and meningitis among other manifestations [7]. World Health Organization (WHO) and British guidelines class the early latent phase of syphilis as infection of less than two years duration, as determined by history and serological results [8, 9]. However the American Centers for Disease Control (CDC) and European (IUSTI) guidelines classify infections acquired less than one year

with no symptoms as early latent and those beyond this as late latent syphilis [10, 11]. Late syphilis consists of late latent (asymptomatic) and tertiary syphilis. Approximately 30- 40% of cases untreated syphilis will develop late symptomatic disease [12]. All those diagnosed with late latent syphilis should have a full examination for clinical evidence of tertiary syphilis. Tertiary syphilis is the manifestation of long term syphilis and consists of cardiovascular, neurological or gummatous involvement. Gummatous syphilis can cause benign lesions in skin, bone, liver and upper respiratory tract. Cardiovascular syphilis primarily involves the aorta leading to aortitis, aortic regurgitation or aneurysm. Late neurosyphilis manifests as meningitis, stroke, cranial nerve palsies, myelopathy (including tabes dorsalis), seizures or progressive dementia (general paresis). Late latent syphilis is diagnosed in the absence of neurosyphilis and other symptoms and signs of disease [13].

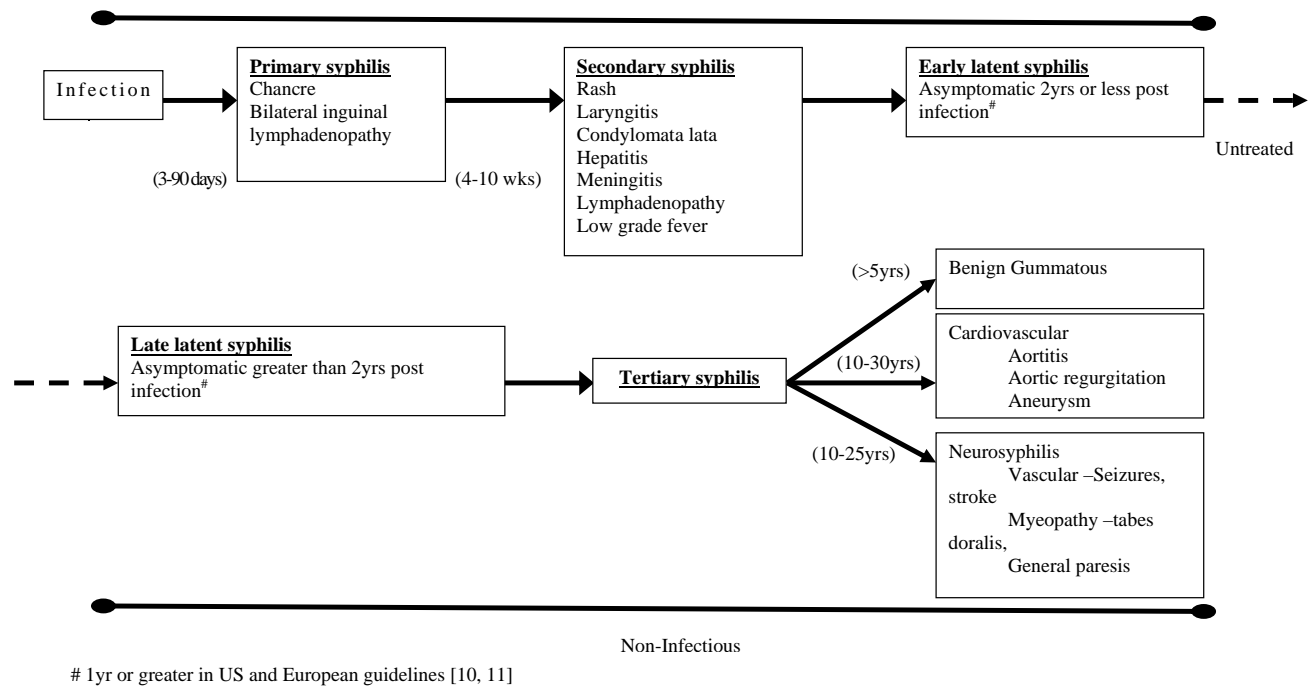
## SYPHILIS IN PREGNANCY

Vertical transmission of syphilis infection may occur during pregnancy leading to fetal infection in at least two thirds of cases, particularly in case of early syphilis in the mother [14]. The outcome will vary depending on the trimester of pregnancy and the stage that syphilis infection occurs. This infection may result in abortion, stillbirth, premature delivery, low birth weight or congenital syphilis. Congenital syphilis can be divided into early (less than two years) and late where the features of congenital syphilis are present after 2 years of life. The seriousness of outcomes and the treatable nature of syphilis have lead to the widespread recommendations for screening of all women in early pregnancy [9-11].

## DIAGNOSIS

The causative organism, the spirochete *Treponema pallidum*, cannot be easily cultured or identified under a standard microscope therefore the diagnosis depends very much on special techniques and serology. The exudates from primary chancres or from the mucous membrane lesions of secondary syphilis may be examined using dark field microscopy for characteristic movement and morphology [15]. The direct demonstration of spirochetes using dark

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**Fig. (1).** Stages of Syphilis.

field microscopy allows immediate diagnosis of early syphilis but is reliant on the clinician suspecting and performing dark ground testing of lesions. Dark field microscopy is less reliable on mucous membrane lesions due to the presence of morphologically similar saprophytic spirochaetes. Immunofluorescence is more sensitive and does not have to be carried out immediately [15]. While darkfield examination and immunofluorescence provide direct evidence of infection they are not widely available.

More commonly syphilis is diagnosed using a combination of treponemal and non-treponemal serological tests. Serological tests will provide only presumptive results as the organism is not directly identified.

Non treponemal testing include the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) tests. These are sensitive tests that are easily analyzed, inexpensive and reliable. Specificity is variously reported as 93-98% with sensitivity varying with stage of disease [16]. 13-41% of tests will be negative in early disease and sensitivity of 60-75% has been reported in late syphilis [17]. A quantitative test may be obtained and the titre level can then be monitored giving a useful tool to chart response to treatment or estimate stage of disease. The non treponemal tests are particularly useful in diagnosis of re infection as most of the other tests remain positive for life once infection established. These tests however are confounded by the possibility of biological false positives which may be transient and can be triggered by various conditions including tuberculosis, pregnancy, autoimmune disease and hepatitis.

Treponemal tests are Treponemal enzyme immunoassay (EIA), *T. pallidum* haemagglutination assay (TPHA), *T. pallidum* particle agglutination (TPPA), fluorescent Treponemal antibody absorption test (FTA-abs), and *T.*

*pallidum* recombinant antigen line immunoassay. Enzyme immunoassays with highly purified *Treponema pallidum* antigens are becoming more commonly used for screening for syphilis. These assays have a high specificity and sensitivity. These usually become positive before non treponemal tests, becoming positive around 2 weeks after infection and usually remain positive lifelong. Sensitivity of EIA IgM is variously reported as 48-77% in early syphilis [16]. Once the TPPA/TPHA are reactive they usually remain so for life and give no indication of current disease activity. Parallel RPR/VDRL titers along with treponemal test results will improve sensitivity of diagnosis. When thinking about a screening Treponemal EIA is currently most widely recommended. Non treponemal tests are not advised because of the delay in development in early stages, the incidence of false positives and the prozone phenomenon [16].

Rapid syphilis point of care (POC) tests have been developed using RPR and immunochromographic based strips (ICS) [18]. The clear benefit is a rapid result facilitating immediate treatment. These are not yet in widespread use but are under evaluation in settings where early diagnosis is important or laboratory facilities and trained personnel are not readily available. The rapid test is a treponemal based test so detect antibodies which tend to persist despite successful treatment thus cannot identify re infection. These POC kits have reported sensitivity ranging from 93.7%-100% and specificity 94.1-100% [19-22].

All sera showing reactive serology on screening tests should be forwarded to a reference laboratory for confirmatory testing and positives should be confirmed with a second specimen. It is necessary to interpret syphilis serology in the context of clinical history, examination and any past record of treatment. It is essential that all cases of syphilis receive close clinical and laboratory follow-up.

Diagnosis of neurosyphilis is centred on clinical findings and cerebrospinal fluid (CSF) analysis. Treponemes will invade the CNS in 25-60% of cases, mostly without symptoms. Lumbar puncture (LP) for the examination of CSF is recommended (see Box 1) in those with positive syphilis serology and ocular, auricular or neurological features suggestive of syphilitic infection. Other situations where a LP should be considered include those who have tertiary disease, disease of unknown duration, those who have failed treatment or those with late latent disease and HIV infection. Some guidelines have also suggested examining CSF of all those with concomitant HIV infection or a serum RPR/VDRL >1:32 [23]. No single test is used in the diagnosis of neurosyphilis but CSF VDRL/RPR is highly specific. The presence of >5/mm<sup>3</sup> mononuclear cells in the CSF along with positive treponemal CSF test suggests the diagnosis of neurosyphilis but cannot be used for interpretation in HIV-infected patients (because they have some degree of pleocytosis at baseline).

#### Box 1.

Lumbar puncture in syphilis is advised when:

- neurological auricular or ophthalmic signs or symptoms
- evidence of active tertiary syphilis
- treatment failure ( clinically or serologically)
- HIV infection with late latent syphilis
- syphilis of unknown duration

Consider if:

- VDRL/RPR >1:32
- HIV infection with CD4 < 350
- Non penicillin treatment

## TREATMENT

Syphilis has been treated with various remedies over the ages. Previous therapy with mercury gave rise to the saying "a night in the arms of Venus leads to a lifetime on Mercury". More recently arsenic was the preferred remedy but since the advent of penicillin in the 1940's this has been the mainstay of syphilis treatment and indeed the first with the ability to cure [24]. Penicillin therapy is generally given intravenously in the form of aqueous crystalline penicillin G or intramuscular as aqueous Procaine or Benzathine penicillin G. The optimal dose or duration of treatment has not been decided by randomised controlled trials rather by experience and observation as was the practice in the former half of 20<sup>th</sup> century. Sexually transmitted infection guidelines differ in their recommendations for preparation, dose and duration of treatment for each stage of syphilis [8-11]. Guidelines are stage based recommending longer durations for the late stages as the treponemes have a slower replicative rate at this point. In the US the CDC recommends single dose Benzathine as the preferred regimen for early syphilis: primary, secondary and early latent syphilis (Table 1) [10]. The UK and European guidelines give the alternative of daily procaine penicillin injections but with variable durations, as well as the Benzathine regimen [9, 11]. Response to treatment is defined as a fourfold drop in nontreponemal titres in a six to twelve month period (6 months in early syphilis, 12 months in late syphilis). Non-penicillin regimens have been constructed using macrolides,

tetracyclines and cephalosporins. These regimens are less well studied but serve as options in penicillin allergic patients or those refusing parenteral treatment. Erythromycin 500mg QDS for 2 weeks has been studied in early syphilis as an oral alternative or for those with penicillin allergy. This course of therapy was associated with high failure rates as it does not cross the blood brain barrier or placenta effectively [25]. Azithromycin as a single dose is another tolerable, very effective option but was found to have resistance levels of 40-90% in several large cohorts [26, 27]. Ceftriaxone has been studied in early disease and crosses the blood brain barrier so may be useful in early or neurosyphilis [28, 29]. However if the patient is penicillin allergic 10% may also react to cephalosporins. Tetracycline is more studied than doxycycline and some of the guidelines reflect this but doxycycline tends to be more widely used as it offers less gastrointestinal side effects with presumed equal efficacy [10, 11].

Pregnant women should be treated with penicillin if at all possible, CDC strongly advises desensitization and penicillin use if allergic. The CDC and BASHH suggest that physicians may wish to give a second dose of 2.4 million units Benzathine one week after the first treatment particularly if treating in the third trimester of pregnancy. These women should not be treated with doxycycline or tetracycline. If using a non penicillin regimen the baby must be treated for syphilis at birth.

There are debates around Benzathine penicillin G use in early disease as it does not penetrate the CSF, resulting in inadequate CSF treponemicidal levels, and possibly explaining treatment failures [10]. Parenteral Penicillin G is the only therapy with documented efficacy for neurosyphilis [30]. No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis or syphilis in pregnancy. In all these scenarios desensitizing and treating with a penicillin based regimen is the preferred treatment option [10]. The aim of treating late stage syphilis is to prevent further complications because if tertiary syphilis is manifest treatment is unlikely to impact this. Again the main stay of treatment of late latent or tertiary syphilis is penicillin, but the regimens are much longer to cover the slower replication rate of the treponemes at this stage. The alternative regimens are listed (Table 1) for use when penicillin options have been explored and are not appropriate.

There are three important reactions to this treatment that need to be remembered and discussed carefully with the patient. The most immediate reaction is anaphylaxis to penicillin and for this reason some guidelines advise the availability of resuscitation facilities and close observation after administration [9, 11]. The second is the Jarisch-Herxheimer reaction. It is unique to syphilis and comprises acute febrile reaction with chills, headache and myalgia commencing within and limited to the first 24hrs. This systemic reaction is believed to be due to significant release of cytokines when large numbers of *T. pallidum* are killed by antibiotics. This may be serious in pregnancy or those with ocular, cardiac or neurological lesions. Some have advised the pre-emptive use of steroid in these situations with 40-60mg Prednisolone daily for 3 days [9, 11]. There is no evidence that steroid reduces morbidity but may decrease

**Table 1. Comparison of Guidelines for Treatment of Syphilis by Stage**

Stage	CDC: American [10]	BASHH: UK [9]	IUSTI: European [11]
Early syphilis (primary, secondary, early latent) (inc pregnancy) 1 <sup>st</sup> line recommendation	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM STAT</li> </ul>	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM STAT</li> <li>• Procaine 600,000U IM 10 days</li> </ul>	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM STAT</li> <li>• Procaine 600,000U IM 10-14 days</li> </ul>
Early syphilis (primary, secondary, early latent) Alternate recommendation	<ul style="list-style-type: none"> <li>• Doxycycline 200mg daily PO 14days</li> <li>• Tetracycline 500mg QDS PO 14days</li> <li>• Ceftriaxone 1g IM or IV 8-10days</li> <li>• Azithromycin 2g PO #</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 100mg BD PO 14days</li> <li>• Azithromycin 2g PO #</li> <li>• Erythromycin 500mg QDS PO 14 days</li> <li>• Ceftriaxone 500mg IM 10days</li> <li>• Amoxicillin 500mg QDS PO + Probenecid 500mg QDS 14 days</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 200mg daily PO 14days</li> <li>• Tetracycline 500mg QDS PO 14days</li> <li>• Erythromycin 500mg QDS PO 14 days</li> <li>• Azithromycin 2g PO #</li> </ul>
Late syphilis (late latent, tertiary) 1 <sup>st</sup> line recommendation	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM 0,1,2 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM 0,1,2 weeks</li> <li>• Procaine 600,000U IM 17 days</li> </ul>	<ul style="list-style-type: none"> <li>• Benzathine 2.4MU IM 0,1,2 weeks</li> <li>• Procaine 600,000U IM 17-21 days</li> </ul>
Late syphilis (late latent, tertiary) Alternate recommendation	<ul style="list-style-type: none"> <li>• Doxycycline 100mg BD PO 28 days</li> <li>• Tetracycline 500mg QDS PO 28 days</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 100mg BD PO 28 days</li> <li>• Amoxicillin 2g TDS PO + Probenecid 500mg QDS 28 days</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 200mg daily PO 21-28 days</li> <li>• Tetracycline 500mg QDS PO 28 days</li> <li>• Erythromycin 500mg QDS PO 28 days</li> </ul>
Neurosyphilis	<ul style="list-style-type: none"> <li>• Benzyl penicillin 18-24 MU IV (3-4MU every 4 hrs) for 10-14 days</li> </ul>	<ul style="list-style-type: none"> <li>• Procaine 1.8-2.4MU IM + Probenecid 500mg PO QDS 17 days</li> <li>• Benzyl penicillin 18-24 MU IV (3-4MU every 4 hrs) for 17days</li> </ul>	<ul style="list-style-type: none"> <li>• Benzyl penicillin 12-24 MU IV (3-4MU every 4 hrs) for 18-21 days</li> <li>• Procaine 1.2-2.4MU IM + Probenecid 500mg PO QDS 10-17 days</li> </ul>
Neurosyphilis Alternate recommendation	<ul style="list-style-type: none"> <li>• Procaine 2.4MU IM + Probenecid 500mg PO QDS 10-14 days</li> <li>• Ceftriaxone 2g IM/IV 10-14days</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 200mg BD PO 28 days</li> <li>• Amoxicillin 2g TDS PO + Probenecid 500mg QDS 28 days</li> <li>• Ceftriaxone 2g IM/IV 10-14day</li> </ul>	<ul style="list-style-type: none"> <li>• Doxycycline 200mg BD PO 28 days</li> </ul>
Pregnant penicillin allergic	<ul style="list-style-type: none"> <li>• Desensitized and treated with penicillin as above</li> </ul>	<ul style="list-style-type: none"> <li>• Amoxicillin 500mg QDS PO + Probenecid 500mg QDS 14 days</li> <li>• Ceftriaxone 500mg IM 10days</li> <li>• Erythromycin 500mg QDS PO 14 days +treatment of neonate at birth with penicillin</li> </ul>	<ul style="list-style-type: none"> <li>• Consider desensitization</li> <li>• Erythromycin 500mg QDS PO 14 days + re-treat mother with doxycycline at delivery</li> <li>• Ceftriaxone 500mg IM 10days (not if anaphylaxis with penicillin)</li> </ul>
HIV	<ul style="list-style-type: none"> <li>• Stage appropriate as for non-HIV infected</li> </ul>	<ul style="list-style-type: none"> <li>• Stage appropriate as for non-HIV infected</li> </ul>	<ul style="list-style-type: none"> <li>• Stage appropriate as for non-HIV infected</li> </ul>

MU: Million units, QDS: 4 times per day, PO: Orally, BD: Twice daily, IM: Intramuscularly, IV: Intravenously, # only use when no other options as high levels of resistance reported.

inflammation. The other event is procaine reaction or procaine psychosis. This manifests as extreme anxiety with a feeling of impending death. Sometimes there are hallucinations, disorientation, and depersonalization. The reaction is self-limiting and usually resolves in less than 20 minutes. The reaction is thought to follow accidental intravenous administration of procaine penicillin. Supportive treatment is usually sufficient but patients should be reassured and if necessary restrained.

Patients will need careful clinical and serological evaluation after treatment, recommended at 3, 6 and 12 months. This is to ensure adequate response to treatment and is done using serial nontreponemal titres. An important part

of management involves identification and treatment of sexual partners. These persons should be given empirical treatment if exposure has been within 90 days of infectious syphilis. All people diagnosed with syphilis should have the condition fully explained and be offered screening for other sexually transmissible infections (STIs). Testing for HIV infection with follow up testing in 3 months is important as there is a high rate of co infection. This contact with health care provides a good opportunity to assess risk and discuss prevention of STIs. Other prevention services available may be highlighted at this time; these may include hepatitis A and B vaccination, post exposure prophylaxis for sexual exposure to HIV infection.

Syphilis remains as an important cause of morbidity, mortality and a possible transmission factor in the spread of HIV infection. With the increasing prevalence of infectious syphilis clinical vigilance and increased testing for syphilis is warranted. The quality of serological diagnosis is improved by using a combination of treponemal and non treponemal tests; this is common practice after a positive screening result is obtained. Further development of point of care screening kits currently underway will aid with expansion of screening programs. Effective treatment is widely available in the form of penicillin. However the therapeutic options for those patients allergic to penicillin are limited. There is a need for further evaluation in large scale randomized controlled trials of treatment regimens, in particular regimen dose and duration and penicillin alternatives.

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