

# **UK National Guideline for the Management of Late Syphilis**

**Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases).**

## Introduction

Late syphilis is defined as infection with *Treponema pallidum* of more than two years' duration.

## Clinical Features

Late syphilis can be broadly divided into two groups. Late latent syphilis is *T. pallidum* infection of more than two years duration diagnosed on serological testing with no symptoms or signs (including cerebrospinal fluid (CSF) abnormalities) of late manifestations of syphilis. Studies of cohorts of untreated patients suggest that symptomatic late syphilis is found in up to 40% of individuals with late *T. pallidum* infection<sup>1</sup>. This consists of three major clinical manifestations, which may co-exist: neurosyphilis; cardiovascular syphilis; gummata.

- Neurological syphilis may be subdivided into two broad groups. Asymptomatic neurosyphilis is diagnosed when individuals have late syphilis with abnormal CSF examination but with no associated neurological symptoms or signs. Symptomatic neurosyphilis is a protean disease consisting of a number of neurological syndromes usually due to direct central nervous system infection by *T. pallidum* or *T. pallidum* associated endarteritis. The most common manifestations of symptomatic neurosyphilis are related to dorsal column loss (tabes dorsalis) and dementia (general paralysis of the insane/GPI) and meningovascular involvement although it has been suggested that in the antibiotic era more subtle and atypical presentations occur more often<sup>2</sup>.
- Cardiovascular syphilis is characterised by an aortitis, which usually involves the aortic root but may affect other parts of the aorta usually spreading distally from the aortic root. The most frequent clinical manifestations of aortitis associated with late syphilis are aortic regurgitation, aortic aneurysm and angina.
- Gummata are inflammatory fibrous nodules or plaques, which may be locally destructive. They can occur in any organ but most commonly affect bone and skin.

## Diagnosis

Diagnosis of late syphilis is based on a combination of positive *T. pallidum* serology (e.g. a positive enzyme-linked immunosorbant assay –EIA- screening test confirmed by *Treponema pallidum* particle agglutination/*Treponema pallidum* haemagglutination assay - TPPA/TPHA or fluorescent treponemal

antibody FTA-abs or a positive TPPA/TPHA screening test confirmed by EIA or FTA-abs) with or without positive non-treponemal tests (VDRL/RPR) and a careful clinical assessment (see early syphilis guideline.) This should include a history focusing on previous syphilis treatment and possible symptoms of early and late manifestations of syphilis. A history to identify previous clinical manifestations and testing for syphilis (antenatal screening, obstetric history, blood donation, and STI clinic attendance) may also aid staging of infection. A clinical examination should be undertaken to exclude both early syphilis and the clinical manifestations of late infection. The examination should seek to identify the common manifestations of early syphilis such as genital and mucosal ulceration, skin rash and general lymphadenopathy. Clinical assessment for the manifestations of late syphilis should be guided by the history but should include examining for aortic regurgitation, pupillary changes (Argyll-Robertson pupils) and dorsal spinal column impairment. Examination should also attempt to exclude the presence of signs of congenital syphilis and the stigmata of yaws if this is a possible differential diagnosis.

Patients with positive syphilis serology with no adequate history of documented treatment and cure in the past and with no evidence to exclude reinfection should be assumed to have active syphilis. This therapeutic strategy should ensure that patients with active syphilis are not left untreated. But patients should have the rationale of this approach clearly explained, as it will entail possible unnecessary treatment of previously treated infections and possible misdiagnosis such as patients with yaws.

### Neurosyphilis

All patients with positive syphilis serology who have neurological symptoms or signs should undergo CSF examination. Some clinicians also recommend CSF examination for those with gummata or cardiovascular syphilis as these individuals have a higher incidence of neurosyphilis.<sup>1</sup> In order for these tests to be interpreted accurately it is important that the CSF is not significantly (macroscopically<sup>3</sup>) contaminated with blood. Almost all individuals who have symptomatic neurosyphilis have a positive non-treponemal (VDRL or RPR) CSF test and a raised CSF white cell count ( $> 5 \text{ cells/mm}^3$ )<sup>2</sup>. Some experts believe that the FTA test should be performed on the CSF. Although the FTA has a lower specificity for diagnosing neurosyphilis than the VDRL/RPR it may be more sensitive and so if negative would usually exclude a diagnosis of neurosyphilis<sup>2</sup>. A negative CSF TPHA would also usually exclude a diagnosis of neurosyphilis. It has been suggested that CSF TPPA/TPHA titres may be useful in excluding a diagnosis of neurosyphilis. A diagnosis of neurosyphilis is unlikely if the CSF TPPA/TPHA titre is less than 320.<sup>4</sup> Some authorities recommend using an albumin corrected ratio of

serum and CSF TPHA titre (the “TPHA Index”) to identify local antibody production within the CNS to improve the sensitivity and specificity of the diagnosis of neurological disease, however this is presently not widely used.<sup>5</sup>

It has been reported that occasionally individuals with neurosyphilis have negative CSF non-treponemal tests with a raised CSF white cell count as the only sign of active infection<sup>2</sup>.

### Cardiovascular Syphilis

This diagnosis is made by the presence of the typical clinical features of cardiovascular syphilis (see above) combined with positive syphilis serology. In addition to a careful examination to exclude clinical evidence of aortic regurgitation, all patients with suspected late syphilis should have a chest X-ray to exclude evidence of an aortic aneurysm. Patients with suspected cardiovascular syphilis need review and assessment by a cardiologist.

### Gummata

Diagnosis of syphilitic gummata is usually made on clinical grounds; typical nodules/plaques or destructive lesions in individuals with positive syphilis serology. Histological examination of the lesions may suggest this diagnosis and very occasionally *T.pallidum* may be identified within the nodules by immunofluorescence.

### The Jarisch-Herxheimer Reaction

Although much less common than in early syphilis (see Early Syphilis Guidelines), this can occur in late infections shortly after administration of the first dose of therapy. There is concern that in late syphilis this reaction might be associated with local oedema around syphilis lesions. If this occurs in vital areas such as the coronary ostia and CNS it may have critical acute consequences. It has been suggested that all patients with symptomatic late syphilis should be treated with corticosteroids to reduce the risk of this phenomenon (evidence level IV,C). Although there is little published evidence to support this therapy, a dose of prednisolone 10-20 mgs PO TDS for three days commencing one day prior to syphilis treatment has been reported to reduce the febrile episode associated with the Jarisch-Herxheimer reaction in early syphilis.<sup>6</sup>

### Management

## Basic Principles

- All patients with syphilis should have a screen for other STIs
- The treatment of first choice for late syphilis is penicillin<sup>7</sup>. Penicillin desensitisation may be considered for patients reporting penicillin allergy<sup>8</sup> (See appendix1). Many people reporting penicillin allergy will not display hypersensitivity on re-exposure to penicillin either because the hypersensitivity has faded or they were never allergic to penicillin. A careful history may help to identify the latter group. Skin testing to confirm allergy should precede desensitisation. (See appendix 2). Skin testing and desensitisation do carry risks of anaphylaxis and should be carried out with immediate access to resuscitation equipment and expertise. Desensitising pregnant women should be undertaken in close collaboration with the obstetric team.
- The penicillin-based regimes are safe to use in pregnancy and breast-feeding.
- It is recommended that all patients presenting with late syphilis have HIV testing. It is thought that HIV may modify the natural history of syphilis with a more rapid progression to neurosyphilis.<sup>9</sup> It has been suggested that there is an increased risk of treatment failure in HIV infected individuals with early syphilis who are treated with benzathine penicillin but there are no controlled trials of benzathine or any other therapies in late syphilis. It has been proposed that asymptomatic individuals with co-infection of HIV and late syphilis should be treated with procaine penicillin regimes as neurological involvement may be more common<sup>10</sup> although this is not supported by evidence.
- There is debate on the importance of CSF examination in asymptomatic patients. A study of risks and benefits of lumbar puncture in this group has suggested that this is not indicated<sup>11</sup> and a wide range of penicillin doses appear efficacious in preventing clinical progression of asymptomatic neurosyphilis<sup>12</sup>. A randomised controlled trial of benzathine penicillin which does not usually produce treponemocidal CSF levels versus a therapy which produces treponemocidal levels in the CSF showed no increased risk of progression from early syphilis to neurosyphilis even in those individuals with *T. pallidum* in the CSF<sup>13</sup>. The CDC guidelines do not recommend CSF examinations for asymptomatic HIV antibody negative patients with syphilis<sup>10</sup>. They do recommend that HIV positive patients with late syphilis should be offered CSF examination in view of the possibly faster evolution of late disease in this group.<sup>6</sup> CSF examination should also be considered for individuals with neurological (including ophthalmological) symptoms or signs, and people with gummata and cardiovascular disease. In the absence of CSF examination some clinicians may prefer to treat asymptomatic late syphilis with the same therapies as neurosyphilis while others may prefer to use a regimen for late latent syphilis.
- Procaine penicillin dose. For neurosyphilis 2.4g (2.4 MU) IM OD of procaine penicillin is the favoured dose in the CDC 1998 guidelines<sup>10</sup> as it has been shown to produce treponemocidal

levels in the CSF, <sup>14</sup>although another study has indicated that this may be an inconsistent finding<sup>15</sup>. However it is likely that lower doses of procaine penicillin (1.8-2.4gm OD) are as efficacious so a range of possible doses is given to reflect this and the available formulations of this drug<sup>13</sup>. Successful completion of a 17 day course has been demonstrated to be delivered consistently in a United Kingdom GUM setting<sup>16</sup>.

## Drug Treatment

### Late latent syphilis

First line therapies:

- Procaine penicillin 0.75 gm IM OD for 17-days<sup>17</sup> (evidence level III, level of recommendation B)
- Benzathine penicillin 2.4 g IM weekly for two weeks (three doses) (III, B).

Second line therapies:

- Doxycycline 200 mgs PO BD for 28 days. For use in individuals who are allergic to penicillin and those declining parenteral therapy (IV, C). Doxycycline 100 mgs PO BD for 28 days is probably sufficient treatment, but the higher dose is usually well tolerated and allows better therapeutic safety if doses are missed.
- Amoxicillin 2 gms PO TDS plus probenecid 500mg QDS for 28 days.<sup>18</sup> (III,C)

### Cardiovascular Syphilis

- Drug therapy: as for late latent syphilis<sup>17,19</sup> (assuming neurosyphilis has been excluded - see above).
- Other Management Considerations: All patients with suspected cardiovascular syphilis should be treated with the drug therapy as above and also should be reviewed by a cardiologist.  
Cardiovascular lesions may progress despite adequate treatment for syphilis.
- All patients with cardiovascular syphilis should be reconsidered for corticosteroid cover at the start of therapy (see Jarisch-Herxheimer reaction).

### Gummata

- Drug Therapy: as for late latent syphilis<sup>17</sup> (assuming neurosyphilis has been excluded).
- Other management considerations: Follow up depends on the extent and site of the gummata.  
Gummata affecting vital organs should be managed in collaboration with the appropriate specialist.

### Neurosyphilis

First line drug therapy:

- procaine penicillin 2gm IM OD plus probenecid 500 mgs PO QDS for 17 days<sup>14</sup>(III, C).

- Alternative regime: Benzylpenicillin 18-24 MU daily, given as 3-4 MU IV every four hours for 17 days (III, C).

Second line therapies:

- Doxycycline 200 mgs PO BD for 28 days<sup>20</sup> (IV, C).
- Amoxicillin 2 gm PO TDS plus probenecid 500 mgs PO QDS for 28 days<sup>18</sup> (IV,C)

NB All patients with neurological syphilis should be considered for corticosteroid cover at the start of the therapy (see Jarisch-Herxheimer reaction).

### Procaine Toxicity

See Early syphilis guidelines

### Follow - up

All patients should be reviewed after the treatment course is finished to ensure adherence with therapy and to follow up partner notification activity (see below). Those patients who present with symptoms or signs related to late syphilis require on-going clinical assessment. Patients who have positive non-treponemal tests (RPR/VDRL) should be checked serologically at six monthly intervals until these are unchanged on consecutive visits (the patient becomes “serofast”).

In patients with neurosyphilis, those found to have CSF abnormalities at diagnosis should have repeated CSF examination six monthly until the cell count is normal. The possibility of treatment failure should be considered if there is one or more of the following factors: clinical progression; increase in non--treponemal test titres by two or more dilutions; failure of CSF pleocytosis to resolve.

### Management of contacts

Individuals with late latent syphilis are usually unable to transmit the infection to sexual partners. Although vertical transmission may occur at any time within 10 years of initial infection, this becomes unusual more than 2 years after the onset of early syphilis.

Because a previous negative sample would significantly affect disease staging and partner notification activity a serious attempt to locate previous syphilis serology testing (antenatal, GUM, blood donation etc) should be made.

These basic principles should inform partner notification activity and it is reasonable for sexual partners and children born to women diagnosed with late latent syphilis of unknown duration to undergo

serological screening with treponemal and non-treponemal serological tests to diagnose or exclude the infection.

The usual minimum incubation periods between initial infection and development of late symptomatic syphilis may be used to inform partner notification activity. These are gummata 2 years, neurosyphilis (tabes dorsalis and GPI) 15 years and cardiovascular syphilis 10 years. This can only act as a guide as accurate diagnosis of late syphilis is often difficult and shorter incubation periods have been described, particularly in association with HIV infection.

#### Auditable Outcome Measures:

1. Contact management of partners and children initiated on all patients with untreated syphilis
2. All patients with suspected neurosyphilis have CSF examination.
3. All patients with positive non-treponemal tests (RPR or VDRL) at diagnosis should have six monthly serology taken until serofast or negative.
4. All patients with syphilis should have had an HIV test.

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Conflict of interest:

None

Evidence Base

This guideline was obtained by searching the Medline database from 1966 up until May 2001 and EMBASE from 1980 to May 2001. The MeSH headings: neurosyphilis; cardiovascular syphilis; latent syphilis were each entered individually into a combined search with the freetext searches of “therapy” and “treatment”. A freetext search combining “gumma\*” with “treatment” and “therapy” was also undertaken. A comprehensive review of syphilis therapy conducted in 1989<sup>21</sup> as preparation for the development of the Centres for Disease Control (CDC) guidelines was examined to obtain key references published before 1966.

As few controlled trials of therapy for late syphilis have been published, clinical experience and expert opinion must guide treatment. The CDC STI guidelines of 1998<sup>10</sup> are used as a source for this expert consensus.

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Table 1. Drugs used in the management of syphilis - Summary

Drug	Dose	Route	Length of treatment
<u>Primary/Secondary/early Latent Syphilis</u>			
Benzathine Penicillin	2.4 g	IM	Single dose or 1 week (two doses of 2.4gm given 1 week apart)
Procaine Penicillin	750mgs OD	IM	10 days
Doxycycline	100mg BD	PO	14 days
Erythromycin	500mg QDS	PO	14 days
<u>Asymptomatic Late Syphilis</u> (No lumbar puncture performed)			
Procaine penicillin	750 mg OD	IM	17 days
Benzathine Penicillin	2.4 g weekly	IM	2 weeks (three doses)
Doxycycline	200 mg BD	PO	28 days

Drug	Dose	Route	Length of treatment
<u>Cardiovascular syphilis</u> (consider steroid cover) Assuming neurosyphilis excluded – as for asymptomatic late syphilis			
<u>Gummata</u> Assuming neurosyphilis excluded – as for asymptomatic late syphilis			
<u>Neurosyphilis</u> (consider steroid cover)			
Procaine Penicillin	2.0 gm OD	IM	17 days
plus Probenecid	500 mg QDS	PO	17 days
Benzylpenicillin	0.3-0.4 gm 4 hourly (1.8-2.4gm/day)	IV	17 days
Benzylpenicillin	0.5 gm 6 hourly (2 gm /day)	IM/IV	17 days
plus Probenecid	500 mg QDS	PO	17 days
Doxycycline	200 mg BD	PO	28 days
Amoxicillin	2 gm TDS	PO	28 days
plus Probenecid	500 mg QDS	PO	28 days

+ Procaine penicillin is only available in the UK in the form of Jenacillin A which contains both procaine and benzyl penicillin G. One vial of Jenacillin A contains 1.5gm of procaine penicillin G and 0.3gm of benzyl penicillin G sodium. 4.5 ml of water for injection is added to the vial to produce 6 ml after constitution. The benzyl penicillin dose is ignored and the dosage of procaine penicillin is calculated to the next whole ml for ease of administration.

+ + Benzathine penicillin and Jenacillin A are not readily available in the United Kingdom but can be imported from France and ordered from IDIS Ltd World Medicines, Mill Bank House, 177-185 Ewell Rd, Surbiton, Surrey, KT6 6AX. Tel: (020) 8410 0710, Fax: (020) 8410 0800, Email: hospitals@idis.co.uk

+ + + Probenecid is an unlicensed drug in the United Kingdom and is also available via IDIS (as above)

N. B. As Jenacillin A, Benzathine penicillin and Probenecid will be obtained from overseas on a named patient basis, it is important that each clinic/pharmacy keeps a log of which patients received these drugs.

## Appendix 1. Penicillin Desensitisation

Desensitisation and a state of unresponsiveness by host cells to specific antigen may be induced with increasing doses of antigen. Using phenoxymethylpenicillin (penicillin V) by the oral route, a safer desensitisation procedure than with parenteral benzylpenicillin, Wendel et al (1985)<sup>12</sup> have followed a protocol (Table) which was effective therapeutically in pregnant women with syphilis. In this procedure an elixir of phenoxymethylpenicillin was given orally in doses of initially 0.059 mg (approximately equivalent to 0.06 mg or 100 i.u. of benzylpenicillin) and increasing by approximately doubling the oral dose every 15 minutes for 14 doses. During the desensitisation procedure in hospital intravenous lines were established and close personal medical supervision was maintained for 24 hours. Mild cutaneous reactions were allowed to resolve spontaneously or were treated with diphenhydramine 25 mg intravenously. After the desensitisation process patients were able to tolerate intramuscular benzathine penicillin treatment in doses appropriate to their infection although close observation was given on re-admission for an oral test dose of 236 mg phenoxymethylpenicillin (equivalent to 240 mg or 400 000 i.u. of benzyl penicillin) followed by observation for 1 hour. The injection of benzathine penicillin was then given and the patients monitored overnight.

Table: Oral desensitisation for penicillin protocol for patients with a positive skin test (Wendel *et al* 1985,<sup>8</sup> with permission).

Phenoxymethyl penicillin dose*	Amount (units per ml)	Volume (ml)	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

\* Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose: 1.3 million units.

## Appendix 2.

Penicillin allergy skin testing (Saxon *et al* 1987<sup>21</sup>, with permission).

Reagents:

*Major determinant:*

- Benzylpenicilloyl poly-L-lysine (Pre-Pen, Taylor Pharmacal Company, Decatur, Illinois) ( $6 \times 10^{-5}$  M).

*Minor determinants:*

- Benzylpenicillin G ( $10^{-2}$  M, 3.3 mg/ml, 6000 units/ml),
- Benzylpenicilloate ( $10^{-2}$  M, 3.3 mg/ml),
- Benzylpenilloate (or penicilloyl propylamine) ( $10^{-2}$  M, 3.3 mg/ml).

Positive control:

- Commercial histamine for epicutaneous skin testing.

*Negative control:*

- Diluent used to dissolve other reagents, usually phenol saline.

Procedures

The use of antihistamines before testing should be avoided (for example, chlorpheniramine).

Discontinue for at least 24 hours before testing.

Patients with a history of penicillin anaphylaxis or those receiving  $\beta$ -adrenergic blocking agents should be tested with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. Otherwise if the patient has had another type of immediate reaction to penicillin within the preceding year, the antigens should be diluted 10-fold.

*Epicutaneous (prick) tests*

Duplicate drops of skin-test reagents are placed on the ventral aspects of the forearm. The underlying epidermis is pricked with a fine needle (26-gauge) without drawing blood. The test is positive if the average wheal diameter after 15 minutes is 4 mm larger than that of negative controls. The histamine controls should be positive.

*Intradermal tests*

If the epicutaneous tests are negative, duplicate 0.02-ml intradermal injections of negative control and antigen solutions are made into the ventral aspects of the forearm, using a 26-gauge needle on a syringe. A test is positive if the average wheal diameter 15 minutes after injection is  $\geq 2$  mm larger than the negative controls.