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Management Issues in Syphilis

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Abstract

Syphilis is a sexually transmitted infection which is systemic from the outset and has increased in incidence worldwide over the last decade. There has been concern as to whether or not co-infection with HIV can modify the clinical presentation of syphilis and, as a genital ulcer disease, it can facilitate the transmission of HIV infection. Diagnosis is based on the microscopic identification of the causative treponeme and serological testing.

Recommendations for the treatment of syphilis have been based on expert opinion, case series, some clinical trials and 50 years of clinical experience. Penicillin, given intramuscularly, is the mainstay of treatment and the favoured preparations for early infectious syphilis are benzathine penicillin as a single injection or a course of daily procaine penicillin injections for 10 to 14 days. The

duration of treatment is longer for late syphilis. There has been concern that benzathine penicillin may not prevent the development of neurosyphilis but that is a rare outcome with this therapy. The main alternative to penicillin is doxycycline, but the place of azithromycin and ceftriaxone is yet to be established.

It is not necessary to carry out examination of the cerebrospinal fluid in patients with early infectious syphilis but it should be performed in those with neurological or ocular signs, psychiatric signs or symptoms, when there is evidence of treatment failure and in those who are co-infected with HIV.

Follow-up is an essential part of management and should be particularly assiduous, for at least 24 months, in those co-infected with HIV. Partner notification should be mandatory to try to contain the spread of infection.

Syphilis is a sexually transmitted infection (STI): 'due to *Treponema pallidum*, (subspecies *pallidum*); of great chronicity; systemic from the outset; capable of involving practically every structure of the body in its course; distinguished by florid manifestations on the one hand and years of completely asymptomatic latency on the other; able to simulate many diseases in the fields of medicine and surgery; transmissible to offspring in man *[sic]*; transmissible to certain laboratory animals; treatable to the point of presumptive cure'.[1]

Syphilis may be either congenital (intrauterine infection) or acquired. The stages are temporal and are delineated in table I. Because of the rarity of syphilis in the industrialised world in the last 30 to 40 years, many younger doctors are not acquainted with its protean manifestations and may not be conversant with the serological tests for syphilis.

While syphilis has retained a relatively low level of endemicity in the non-industrialised world, after the advent of penicillin and the antibiotic era in the mid 1940s, it ceased to be a major health problem in the industrialised world except in particular high risk groups such as homosexual men. However, there has been a recrudescence of the infection over the last decade in many parts of Europe and North America, particularly in the Russian Federation and its adjacent countries. In 1999, the World Health Organization (WHO) estimated that, worldwide, there were approximately 12 million new cases of syphilis among adults.[3] In Western Europe, taking England as an example, the incidence was 0.3 per 100 000 of the population,[4] whereas in Russia the incidence was much higher at 900 per 100 000 of the population aged between 20 to 29 years in 1996.[5] In China between 1989 and 1998, the incidence of syphilis increased approximately 20-fold.[6] The situation in an African country, Zimbabwe, was even worse with a incidence of 2300 per 100 000 of the population.[7] Most industrialised countries have reported an increase in incidence within certain populations (particularly men who have sex with men and individuals infected with the human immunodeficiency virus [HIV]) and a number of well defined outbreaks have been identified in England.[8-10]

1. Syphilis and HIV Co-Infection

Syphilis, like many other sexually transmitted infections (STIs), will increase the risk of sexual transmission of HIV but HIV is unique in its ability to modify the clinical presentations of other STIs.[11,12] The former carries great implications for the containment of the global HIV epidemic through STI control, while the latter necessitates a thorough re-evaluation of these genital tract infections in the context of HIV co-infection. Before more definitive information is available, particular attention is needed in the management of patients with co-infection.

As a genital ulcer disease, syphilis increases the rate of HIV transmission by up to five times[12] and, furthermore, it has been demonstrated that treatment of STIs early in an HIV epidemic can be associated with a decline in the incidence of HIV infection.[13] Most often the clinical picture is little different between HIV-infected and HIV-unin-

Table I. Classification of syphilis

Acquired syphilis	
Early infectious syphilis	
Primary syphilis[a]	An often painless anogenital chancre (ulcer) with dependent lymphadenopathy
	Can persist into the secondary stage
	Incubation period of 9-90d but usually 3-4 wks
Secondary syphilis[a]	Multisystem involvement due to bacteraemia, resulting in generalised rash (+/- condylomata lata), and lymphadenopathy, systemic malaise and fever, buccal and genital mucosal erosions; may also cause patchy alopecia, hepatitis, meningitis, cranial nerve palsies, uveitis, periostitis and glomerulonephritis
	4-8 wks after appearance of chancre
Early latent syphilis	From the end of the secondary stage to the end of a 2y period after the appearance of chancre
	Positive STS but without symptoms or signs
	Classified as infectious because relapse to the secondary stage is possible up to 2y
Late non-infectious syphilis	
Late latent	From the 2y point onwards
	Asymptomatic with positive STS
	Most untreated patients would remain in this stage
Gummatous syphilis	Rare but described in patients recently co-infected with HIV;[2] can be infiltrative or ulcerative
Neurosyphilis	Rare but rapid progress to this stage, described in patients co-infected with HIV; meningovascular, tabes dorsalis and general paresis
Cardiovascular syphilis	Rare; aortic regurgitation or aneurysm, coronary ostiitis
Congenital syphilis	
Early congenital syphilis (< 2y)	
Late congenital syphilis including stigmata	

a Some patients do not notice the primary and secondary stages, and infection is only detected on STS.

STS = serological tests for syphilis.

fected hosts. There are studies and case reports, however, suggesting an influence by HIV infection on the clinical presentation of syphilis (table II).

2. Diagnosis

Diagnosis of primary and secondary syphilis is based on:

- Clinical appearances - in those with symptoms and/or signs.
- Direct detection of the causative organism, *T. pallidum* (subspecies *pallidum*). This may be either by visualisation using a dark field microscope or by the direct fluorescent antibody technique (DFA-TP). This latter technique identifies *T. pallidum* in a direct lesion smear by immunofluorescence using polyclonal antiserum but is very labour intensive. A newer molecular technique, polymerase chain reaction (PCR), is not widely available at present and is not standardised, but is likely to be used more in the future.
- Indirect detection through serological testing. There are two groups of tests available: (i) treponemal tests, i.e. treponemal enzyme immunoassay (EIA with immunoglobulin [Ig]G or IgM), *T. pallidum* particle agglutination test (TPPA) or the *T. pallidum* haemagglutination assay (TPHA), fluorescent treponemal antibody-absorbed test (FTA-Abs); and (ii) 'non-treponemal' cardiolipin (reaginic) tests, i.e. Venereal Diseases Reference Laboratory test (VDRL) or the rapid plasma reagin test (RPR).

Many laboratories now use EIA (IgG or IgM) as a screening test, although the TPPA or TPHA together with VDRL or RPR can also be used.[14] Should the EIA be positive, the laboratory will then go on and perform other treponemal tests such as the TPPA or TPHA. In cases of doubt, the FTA-Abs is done too. In addition, a cardiolipin test such

Table II. Clinical aspects of syphilis and HIV co-infection

Primary syphilis may present with larger or more numerous chancres
A primary syphilitic chancre and chronic mucocutaneous herpes (an AIDS-defining diagnosis) may be similar clinically
Secondary syphilis and primary HIV infection can be similar clinically
'Malignant syphilis' (accelerated ulcerating secondary syphilis)
More frequent ocular syphilis
Rapid progression to the late stages of syphilis, particularly neurosyphilis
Atypical presentations of neurosyphilis
Unusual manifestations of gummatous syphilis

as the VDRL or RPR should be carried out. These are useful for quantitating the activity of an infection and in monitoring treatment, i.e. following treatment, the VDRL/RPR titre should fall to negativity or close to it. Failure for that to happen may indicate either a treatment failure, re-infection or, at a low titre the patient may be 'sero-fast'. The treponemal tests are not usually quantitated. Biological false-positive reactions can occur with the 'non-treponemal' cardiolipin tests so it is essential always to perform treponemal tests. In primary syphilis, EIA IgM and FTA-abs are usually the first tests to be positive and should be requested if a chancre is suspected.

Because it is possible for specimen mix-ups to occur, either with the healthcare provider or in the laboratory, a second serum sample should always be sent to confirm a result.

It is important to note that both treponemal and non-treponemal serological tests for syphilis (STS) are also positive in the non-venereal treponematoses such as bejel or endemic syphilis (*T. pallidum* subspecies *endemicum*), in yaws (*T. pallidum* subspecies *pertenue*) and in pinta (*T. pallidum* subspecies *carateum*). The distinction between venereal and non-venereal treponematoses is based on the clinical history, the age and the country of origin of the patient, as well as whether or not there are any signs, often on the skin, of these infections.

The diagnosis of latent syphilis is based on the STS results and a clinical history of when infection might have taken place. A diagnosis of gummatous syphilis is generally based on clinical appearances with positive STS and biopsy of the lesion to exclude other causes. Symptomatic neurosyphilis is diagnosed on the neurological signs and symptoms along with positive STS and examination of the cerebrospinal fluid (CSF). In patients with neurosyphilis, examination and investigation should be carried out to exclude cardiovascular and ocular syphilis.

3. Treatment

Treatment for syphilis has been available from early times but, until the first arsenical became available in 1909, treatment had been predominantly with mercury, given by mouth, injection, inunction or inhalations. Other treatments had included guaiacum, iodides and fever therapy.[15] Arsenicals were augmented by bismuth in the 1920s and this combination was used until Mahoney[16] demonstrated that penicillin was effective in 1943.

At first, injectable benzylpenicillin (penicillin G) was used, but this needed to be given frequently and was very painful if given intramuscularly. One of the first long acting injectable penicillins was procaine penicillin in oil with aluminium monostearate (PAM) which was used extensively in the yaws eradication campaign of the 1950s and 1960s, only one injection being needed. An early oral penicillin, phenoxymethylpenicillin (penicillin V), proved to be unreliably absorbed and, therefore, was dismissed as a suitable agent with which to treat syphilis, although a more recent study in Sweden did show some efficacy.[17] When the newer oral penicillins such as ampicillin and amoxicillin were introduced they were not extensively investigated as the incidence of syphilis, by that time, was very low in the industrialised world and, therefore, the evidence base for their use is limited. Nevertheless, the efficacy of penicillin in the treatment of syphilis was well established through clinical experience prior to the value of randomised, controlled clinical trials being recognised. Thus, most of the recommendations for the treatment of syphilis have been based on

expert opinion, case series, some clinical trials and half a century of clinical experience.

3.1 Penicillin in Early Infectious Syphilis

There is a dearth of adequately conducted comparative trials to guide the selection of an optimal penicillin regimen - not for dose, duration or preparation. Parenteral benzylpenicillin has been used effectively for 5 decades to achieve local cure – healing of lesions and prevention of sexual transmission - and it remains the recommended drug for the treatment of syphilis in most countries.[18-22]

However, the preparation used varies from region to region. In North America, in the Center for Disease Control (CDC) guidelines, the preferred preparation is benzathine penicillin, (the tetrahydrate salt of benzylpenicillin), 2.4 million units intramuscularly in a single dose. In Europe, while the benzathine preparation is also recommended, the procaine salt of penicillin, 600 000 units intramuscularly for 10 to 14 days, is preferred in some countries.[19-21] There are obvious advantages to the use of a single injection; the patient does not have to be persuaded to return for daily penicillin administration and it is, in effect, a one-off directly observed therapy (DOT). Daily procaine penicillin by intramuscular injection is, of course, also DOT. The WHO recommends intramuscular benzathine penicillin as first line therapy, with injectable procaine penicillin as an alternative.[22]

Concern arose about benzathine penicillin in 1976 when two articles appeared in the same issue of *JAMA*,[23,24] one showing persistence of treponemes in CSF after treatment with benzathine penicillin and the other showing that no penicillin was detected in the CSF when two patients who had had positive STS were treated with benzathine penicillin. The editorial which accompanied these papers opined that while the benzathine preparation should be adequate therapy for primary syphilis, once spirochaetaemia has occurred in the secondary stage of syphilis, it must be assumed that the organism will reach the brain and that if benzathine penicillin does not enter the CSF,[25] then we ought to change the method of treatment of late syphilis by using aqueous penicillin. Of course, whether there is penicillin in the CSF does not establish that it is not present in the brain tissue itself.

This led to a plethora of studies investigating penicillin concentrations in the CSF after benzathine and procaine penicillin administration and, at least for neurosyphilis, led to a higher dose being recommended. The inner layer of the bacterial membrane contains peptidoglycan which makes *T. pallidum* highly sensitive to penicillin. From early days a serum penicillin concentration of >0.018 mg/L has been considered treponemicidal, although this is far lower than the maximally effective *in vitro* level of concentration at 0.36 mg/L.[26-28]

Benzathine penicillin has a peak plasma concentration at 13 to 24 hours with an effective concentration maintained for 7 to 10 days. Procaine penicillin, on the other hand, has a peak plasma concentration in 1 to 4 hours with an effective concentration maintained for 12 to 24 hours. To be effective, the treponemicidal concentration should be maintained for at least 7 days to cover a number of division times (30 to 33 hours) of the treponemes in early syphilis, with a sub-treponemicidal interval of not more than 24 to 30 hours.[26] So both benzathine and procaine preparations should be satisfactory, but benzathine penicillin injections can be very painful and to minimise this should be reconstituted with lidocaine and the dose divided between both buttocks. Because the treponemes probably divide more slowly in late disease, a longer duration of treatment is advisable as the duration of infection increases.

Finally, persistent spiral organisms/treponemes have been identified despite apparently adequate treatment.[29,30] Whether or not these can cause a relapse of the infection is not known but is a possibility in immunosuppressed patients.

3.2 Options if a Patient Declines Injectable Therapy

In the industrialised world some patients have an aversion to injectable therapy and, if procaine penicillin is to be used, it necessitates multiple vis-

its for administration. The opposite is true in some regions of the developing world where it is a common belief that medication by injection is superior.

There is most experience with the tetracycline group of drugs, especially tetracycline itself at a dose of 500mg four times daily for 14 days.[18,20] There is less experience with doxycycline but compliance is likely to be better than with tetracycline as it is administered four times daily. Doxycycline can be administered at either 100mg twice daily or as a single dose of 200 mg/day for 14 days.[18,19,21,30] It has also the advantage that dairy products do not have to be avoided. Erythromycin at a dose of 500mg four times daily for 14 days has also been used but the efficacy may be less.[18-21] The well absorbed amoxicillin ought to be effective and has been found to penetrate the CSF well.[31,32] Azithromycin, a newer macrolide antibiotic with a long half life (approximately 68 hours) which is used to treat other STIs (chlamydia) has also been investigated.[33-35] Quinolones are not effective against *T. pallidum*.[36]

3.3 Penicillin Allergy

Doxycycline, tetracycline and erythromycin are the choices, as discussed in section 3.2. Some may wish to consider azithromycin and, if the patient is not averse to injectable therapy, then ceftriaxone may be considered, but most of the evidence for its efficacy is with neurosyphilis (see section 3.5.2). Although a third generation cephalosporin, there is still a slight risk of cross reactivity with penicillin and it should not be used if a patient has a history of anaphylaxis with penicillin. The suggested regimens are azithromycin 500 mg/day and intramuscular ceftriaxone 500 mg/day, both for 14 days. Another option would be to offer penicillin desensitisation, a strategy often recommended for pregnant mothers.[18]

3.4 Late Latent Syphilis

The rationale behind the treatment of this stage of infection is to prevent progression to the late forms of syphilis. Certainly, those who apparently have latent syphilis should be carefully examined for evidence of late/tertiary disease to ensure that a misdiagnosis is not being made. Thus, a careful history and examination should be undertaken looking for gummata (rare at present), neurological, cardiovascular and ocular complications, and aortitis (on a chest radiograph). This might be particularly important in patients co-infected with HIV. Five decades of experience seem to support the effectiveness of therapy but there is little evidence upon which to base decisions regarding specific regimens. The evidence available is in support of penicillin containing regimens but there is little evidence for the use of non-penicillin regimens for the treatment of this stage of the disease.

The same drugs used for early infectious syphilis should be administered, but for a longer duration because of the slower division of treponemes in late disease. Thus, benzathine penicillin 2.4 million units should be given intramuscularly at days 1, 8 and 15.[18-21] Procaine penicillin needs to be given for 17 to 21 days. The CDC guidelines do not recommend this but it has been standard practice in many European countries, usually at a daily dose of 600 000 units intramuscularly.[19-21] Some physicians recommend a large dose of procaine penicillin (1.2 million units) and this may be best for heavier patients.[21]

Where there is penicillin allergy or intramuscular treatment is refused, then doxycycline 200 mg/day (either 100mg twice daily or a single 200mg dose) can be given over 21 to 30 days.[18,19,21] Tetracycline 500mg four times daily for 28 to 30 days or erythromycin 500mg four times daily for 28 days may also be considered.[21,22] These recommendations tend to be passed on from one set of guidelines to another without the support of meaningful clinical trials.

3.5 Late Forms of Syphilis

The definitions of the late forms of syphilis may vary. Gummatous syphilis is sometimes referred to as benign tertiary syphilis, but the CDC guidelines state that tertiary syphilis includes gummatous syphilis and cardiovascular syphilis. Others refer to quaternary syphilis, which includes cardiovas-

cular and neurosyphilis. Some degree of overlap may occur and it is possible to have all three forms of late syphilis. There had been anxiety in the 1960s that, with the aura of antibiotics in the general population, early syphilis would be partially treated by happenstance and that there would be a risk of the late forms of syphilis developing. This has not come to pass. Cardiovascular syphilis remains rare but neurosyphilis continues to be recognised in individuals not infected with HIV but especially those who are infected.[37]

3.5.1 Gummatous Syphilis

As gummatous syphilis is such a rare disease it is difficult to evaluate therapy since there are no controlled studies of penicillin in any large series of patients. The last review of treatment by St John in 1976[38] found no therapeutic trials subsequent to the 1940s and advised that a recommendation made in 1948 still stood - that 'at least 2 million units of penicillin if not more' would be necessary.[39] While the current WHO guidelines do not mention treatment of gummatous syphilis, the CDC guidelines do.[18] There the recommended therapy regimen is intramuscular benzathine penicillin 7.2 million units in total, administered as three doses of 2.4 million units at 1-week intervals. European guidelines[21] concur with this but also suggest the use of intramuscular procaine penicillin 600 000 units daily for 17 to 21 days.[19-21]

3.5.2 Neurosyphilis

The advent of penicillin completely changed the management of neurosyphilis; it simplified it and dramatically improved the outcome.[40,41] Most patients in these trials had initially received less than 6 million units of penicillin. Thus, in the 1960s and 1970s, three doses of benzathine penicillin (total of 7.2 million units) or a 21-day course of procaine penicillin at 600 000 units daily was used (total of 12 million units). But reports in the 1970s,[22,23,42] showed that treponemes could persist in the CSF and that penicillin was not detected in the fluid following the use of benzathine penicillin.[23,24,43] Hooshmand et al.[44] reported patients with tabes dorsalis or meningovascular syphilis where clinical evidence of active neurosyphilis and CSF pleocytosis persisted after the use of the standard regimens of that time. However, an increased dose of procaine penicillin resulted in symptomatic improvement in these patients, although a few patients went on to develop general paresis. Numerous dose ranging studies were performed thereafter, summarised well by Dunlop,[29] to establish what doses were actually needed to produce treponemicidal penicillin concentrations in the CSF.

Currently, the advice is that penicillin should be given either intravenously or, if patient compliance can be relied on and the patient does not require hospitalisation, by intramuscular injection of procaine penicillin. The data concerning the effectiveness of using a procaine penicillin and probenecid combination to produce treponemicidal CSF penicillin concentrations is conflicting.[42,45] The concern that the CSF penicillin concentration is increased at the expense of the CNS tissue concentration[42,46] may not be relevant because concentrations in both the CSF and in CNS tissue are higher with probenecid than without, with a much higher concentration, relatively, in the CSF.[29] However, anecdotally, the use of the procaine penicillin/probenecid combination has been successful in the UK, although the availability of probenecid in some countries is now becoming a problem.

Thus, the recommendations for first-line therapy for the treatment of neurosyphilis are now intravenous aqueous (crystalline) benzyl penicillin 12 to 24 million units daily as 3 to 4 million units every 4 hours over 10 to 21 days.[18-22] The dose may also be estimated on a basis of 0.15 million units/kg/day intravenously, spread over six doses (every 4 hours) for 10 to 14 days.[20,46] An alternative is intramuscular procaine penicillin 1.8 to 2.4 million units daily plus probenecid 500mg four times daily for 10 to 21 days.[18-21,45,47]

Where a patient is penicillin allergic or parenteral treatment is refused then doxycycline 200mg twice daily over 28 to 30 days has been recommended.[19-21,48] The WHO guidelines[22] also recommend oral tetracycline 500mg four times daily for 30 days.

There remains a need for effective alternatives to penicillin, apart from the tetracyclines. The prolonged half-life, adequate CNS penetration and satisfactory activity against *T. pallidum* of ceftriaxone suggest that this drug should be suitable. However, studies in both humans and animal models suggest that ceftriaxone may not be any more efficacious than high-dose penicillin.[49-52]

Patients with auditory disturbances, caused by syphilis, should be treated as described for neurosyphilis. Corticosteroids have been used as adjunctive therapy in otologic syphilis and often resolve the associated tinnitus, sometimes permanently, but usually do not induce a lasting benefit with the hearing loss.

3.5.3 Cardiovascular Syphilis

Some experts treat all patients who have cardiovascular syphilis with a neurosyphilis regimen and this may involve parenteral therapy.[18] The management, other than antibiotic therapy, of the three main problems in cardiovascular syphilis, aortic aneurysm, coronary artery disease and aortic valve disease are beyond the scope of this article but, in general terms, involve a surgical approach. It is said that a Jarisch-Herxheimer Reaction (JHR) consequent upon antibiotic therapy may result in coronary ostial occlusion or even in rupture of a syphilitic aneurysm. Thus, some authorities have recommended the use of corticosteroids to modify this response but there is little evidence to support such a strategy.

3.5.4 Ocular Syphilis

Ocular manifestations are probably uncommon in untreated syphilis, not being mentioned at all in the Oslo study of untreated syphilis,[53] but optic atrophy was found in about 3% of patients in the Tuskagee study.[54] Where there is serious ocular involvement as optic neuritis or neuroretinitis, treatment should be as for neurosyphilis, probably using parenteral therapy.[18,21] Some experts would also give corticosteroid cover to ameliorate the JHR, because of reports of deterioration following treatment. In addition, corticosteroids may already be used in the management of these conditions, unrelated to syphilis, and biological plausibility would suggest that this might help. Syphilitic uveitis of short duration, usually occurring in the secondary stage, may be treated with parenteral benzathine penicillin,[55,56] but preferably as for neurosyphilis.

4. In Whom Should Evaluation of the Cerebrospinal Fluid Be Undertaken?

There is a 30 to 40% likelihood of CSF abnormalities in primary and secondary stage syphilis.[57] This has never been shown to predict progression to neurological complications but the studies previously mentioned,[22,23,42] where treponemes were found to persist following penicillin therapy and where no penicillin was detected in the CSF after administration of benzathine penicillin, have certainly caused concern.

However, years of experience with benzathine and procaine penicillin in early infectious syphilis are reassuring. In addition, in a study of CSF abnormalities in early stage syphilis, although they were found to be common, they were not predictive of treatment failure.[58] CSF abnormalities are common in HIV infection anyway,[59] and in 1987, two papers showing rapid progression from the early stage to neurosyphilis caused alarm.[60,61] Subsequent reports have included similar findings. Whether or not risk can be stratified by the CD4+ count or by the reagin test titre remains to be demonstrated. However, experts now advise that certain individuals co-infected with HIV should have a CSF examination,[18,21] particularly those with latent or late syphilis.

Thus, it might reasonably be suggested that, in individuals who are not infected with HIV and who have early infectious syphilis, it should not be necessary to perform lumbar puncture as long as the individuals do not have neurological symptoms or signs. But in those with any of the forms of late syphilis, especially those with neurological symptoms and signs, CSF examination should be carried out. Patients with positive syphilis serology and psychiatric symptoms should be checked.[62] It is difficult to justify a lumbar puncture for every patient with latent syphilis, apart from those men-

tioned above including those in whom it is intended to use non-penicillin therapy.[63] However, if lumbar puncture is not performed to exclude CSF involvement, one should consider treating patients with regimen as for neurosyphilis. It has not been shown that those with a reagin titre of >1 : 32 are more likely to have CSF abnormalities suggestive of neurosyphilis,[63] however, if a high titre does not decline by 12 to 24 months after therapy, such a patient requires evaluation for neurosyphilis (including CSF examination) and re-treatment. Should the reagin titre increase 4-fold (2 dilutions) after treatment then this should be regarded as a treatment failure and re-treatment should be planned after examination of the CSF. Indications for lumbar puncture are summarised in table III.

The CDC guidelines recommend that if a CSF pleocytosis was present initially, CSF examination should be repeated every 6 months until the cell count is normal. However, non-relevant CSF findings suggesting aggravation due to the so-called paradoxical response may cause unnecessary confusion.[64] In meningovascular neurosyphilis the number of mononuclear cells in the CSF generally normalises faster (6 to 12 months) than parenchymatous neurosyphilis (1 to 2 years). The mononuclear cell count should be normal within 1 to 2 years, but other measurements such as the TPHA-index may remain abnormal and the CSF reagin test may remain positive. For these reasons, follow up CSF examination should not be performed earlier than 1 to 2 years after treatment of neurosyphilis.[21]

Table III. Indications for cerebrospinal fluid (CSF) examination in patients with syphilis

In those with positive STS and neurological or ocular signs/symptoms, the presence of gummata or aortitis
In those with positive STS and psychiatric signs/symptoms
In those with evidence of treatment failure
In those with concomitant HIV infection (late latent syphilis or unknown duration)

STS = serological tests for syphilis.

5. Management of Special Situations

5.1 Incubating Syphilis

As a result of partner notification activity, sexual partners of those with early infectious syphilis may appear for evaluation and treatment. Some may wish to be followed up through the incubation period (up to 3 months) and, if seronegative and asymptomatic at the end of the that time, treatment will not be necessary. However, many wish to be treated epidemiologically/presumptively and intramuscular benzathine penicillin 2.4 million units as a single dose has been recommended.[18]

Azithromycin 1g orally as a single dose has also been investigated in this situation and none of the participants developed syphilis. However, in the study most index patients had early latent and not primary or secondary syphilis.[65]

5.2 Syphilis with HIV Co-Infection

The issue of interaction between syphilis and HIV became topical after two reports in 1987 of co-infected individuals where the syphilis was, apparently, refractory to standard therapy or displayed a rapid progression to neurosyphilis.[60,61] Manifestations of syphilis and HIV can mimic each other. Numerous other reports have described more severe manifestations of syphilis, accelerated progression to late syphilis[2,66-83] especially neuro, ocular[66-81] and gummatous syphilis,[2,82,83] well summarised by Czelusta and colleagues[84] (see also table II). A study by Rolfs et al.[58] showed no increase in the incidence of neurosyphilis in either HIV positive or negative patients treated for early syphilis, although the follow-up period was short. However, the drop-out rate was high with only 52% followed up for 1 year.

STS can mostly be interpreted the same as in individuals without HIV infection, but there have been reports of a higher rate of biological false positive reactions with 'non-treponemal' cardiolipin tests.[85-87] Following treatment the reagin titres will generally fall 4-fold and individuals with HIV infection usually follow this normal pattern.

However, there have been reports of a delayed serological titre response after treatment,[58,88-90] of cases of seronegative syphilis[80,91,92] and of the return of positive STS to negativity as immune suppression advances.[68,93] Thus, if the clinical findings are suggestive of syphilis and the STS are unreactive or unclear, alternative methods of diagnosis should be implemented such as darkfield examination, biopsy and direct fluorescent antibody staining or PCR examination of material from the lesion.[18]

Progression to neurosyphilis despite apparently appropriate therapy has prompted the recommendation to perform CSF examination in latent or late syphilis.[18] Therapy might then be modified, dependent upon the findings. However, most physicians would treat all stages of syphilis in the same manner as in those who are not infected with HIV.[18,20-22] Whether this is effective over time remains to be seen as patients treated with standard therapy have not been followed up for a sufficient period of time. If HIV treatment fails and patients become progressively immunosuppressed, there is concern that persisting treponemes may reactivate. Furthermore, as neurological complications and CSF abnormalities are common in HIV infection *per se*, should neurological symptoms or signs occur in patients treated with standard therapy, the possibility of neurosyphilis resulting from suboptimal treatment arises. In view of this, and of reports of progression to neurosyphilis in patients treated with benzathine penicillin, some physicians would treat all patients infected with HIV as for those with neurosyphilis.

There is concern that serological relapse is more frequent in patients co-infected with HIV[94] but other studies have shown no significant difference from those without HIV co-infection.[95,96] Nevertheless, because of these anxieties, assiduous follow-up for clinical and serological evaluation for treatment failure at 3, 6, 9, 12 and 24 months after therapy is sensible. Although of unproven benefit, some experts recommend CSF examination 6 months after therapy in early infectious syphilis.[18,21]

5.3 Syphilis in Pregnancy

Congenital syphilis is preventable and its occurrence is a reflection of the inadequacy of antenatal services in any country. It has been rare in the industrialised world in recent years, although more prevalent in some resource-poor countries. Its incidence is increasing in countries where the medical infrastructure is in decline, such as in the Russian Federation.[5] In some Western countries there has been debate as to whether or not to abandon antenatal screening for syphilis but it ought to be performed even if only 1 in 10 000 is expected to be positive.[97] All women identified as having syphilis should be offered HIV testing.[98]

The risk of intrauterine infection is greatest in the early infectious stages of the disease in the mother, and rarely occurs after that. Seventy to 100% of infants born to mothers with early infectious syphilis will be infected, with stillbirths in up to one third. If there has been documented proof of adequate treatment and follow-up, demonstrated by a fall in reagin titre prior to pregnancy, it ought not to be necessary to re-treat during the pregnancy unless there is concern about relapse of the infection or re-infection (evidenced by a greater than one dilution or 2-fold rise in reagin titre). However, some mothers prefer the reassurance of re-treatment and physicians concerned for the welfare of the newborn may require similar reassurance.

The preferred treatment of syphilis in pregnancy remains penicillin and it should be administered as in the non-pregnant state, although there is insufficient evidence to support the recommended regimens. In a recent study,[99] a single intramuscular injection of benzathine penicillin 2.4 million units given to mothers with early infectious syphilis produced a 98% success rate in the prevention of congenital syphilis. Treatment failures with benzathine penicillin in pregnant women have been reported.[100-102] One study showed that a single injection did not prevent preterm birth, intrauterine death and congenital syphilis, but a second dose of 2.4 million units did.[102] Treponemicidal activity of less than 3 weeks (the estimated optimal duration of 2.4 million units of benzathine penicillin)

was felt to be insufficient to protect the newborn. Thus CDC and European guidelines recommend two intramuscular doses of benzathine penicillin 2.4 million units, 1 week apart, for early infectious syphilis or intramuscular procaine penicillin 600 000 or 1.2 million units daily for 10 to 14 days,[18,21] and this seems reasonable.

If the patient is penicillin allergic the options are limited. Congenital syphilis has occurred in babies born to mothers given erythromycin, and tetracyclines cannot be used in pregnancy. Some feel that penicillin allergic individuals should be desensitised using escalating doses of phenoxymethylpenicillin and this is clearly described in the CDC guidelines.[18] Ceftriaxone can also be considered if no alternative is available. If erythromycin is used, the baby must be treated with penicillin at birth as erythromycin does not penetrate the placental barrier and consideration given to retreat the mother with doxycycline after delivery.

It is often difficult to be certain when the mother might have acquired syphilis but contact tracing should be undertaken.

The management of congenital syphilis is delineated in the CDC and European guidelines.[18,21]

6. Reactions to Treatment

The three reactions of concern are anaphylaxis, the JHR and the procaine reaction. Patients being treated for early infectious syphilis should be warned about the JHR.

6.1 Anaphylaxis

Facilities for the treatment of anaphylaxis should be available, as penicillin is one of its common precipitating causes. Management is with epinephrine (adrenaline) 1 **:** 1000 0.5mls intramuscularly followed by an antihistamine such as chlorpheniramine 10mg and hydrocortisone 100mg, both either intramuscularly or intravenously.

6.2 The Jarisch-Herxheimer Reaction

The JHR is an acute febrile illness with rigors, headache, muscle aches and a secondary rash appearing or becoming more prominent. It is more common in those treated for early infectious syphilis, and it often starts within 2 hours of administration of the treatment and effects have usually resolved within 24 hours. It is not important unless there is neurological or ophthalmic involvement, and in the second half of pregnancy when it can cause fetal distress and preterm labour. While rare in late syphilis, it could be a problem if the coronary ostia, the larynx or the nervous system including cranial nerves are involved, because of local swelling. Prednisolone at a dose of 10 to 20mg three times daily for 3 days may abolish fever but is unproven in reducing local inflammation,[103] and is given 24 hours before commencing antisyphilitic treatment. As deterioration of affected lesions such as anterior uveitis and optic neuritis following antisyphilitic treatment have been reported and corticosteroids had been used to treat such lesions particularly if 'idiopathic', biological plausibility suggests that it might be useful to reduce inflammation. Systemic treatment with a tumour necrosis factor (TNF) antagonist may be more effective than a corticosteroid.[104]

6.3 The Procaine Reaction

The procaine reaction (procaine psychosis, procaine mania or Hognié syndrome) is a rare event and is believed to occur as a result of inadvertent intravenous injection of procaine penicillin during intramuscular administration. The risk of it occurring may be reduced by aspiration into the syringe following insertion of the needle prior to injection. Should there be any evidence of blood the needle should be replaced in a different site. It is a most alarming reaction and the patient may experience fear of impending death, may hallucinate or even seizure immediately after the injection. They may become violent and possessed of unusual strength and require physical restraint. The reaction rarely lasts more than 15 to 20 minutes. If the patient is convulsing then intravenous, intramuscular or rectal diazepam may be given.

7. Follow-Up

Follow-up is advised to establish that treatment has been effective and to look for evidence of re-infection or reactivation. Apart from clinical assessment, the quantitated non-treponemal (reagin) test should be repeated (VDRL/RPR). In patients with early infectious syphilis, the titre should decline by two dilution steps (4-fold) within 6 months, and perhaps more slowly in patients co-infected with HIV. Thus, follow-up at 1, 3, 6 and 12 months is recommended in early infectious syphilis. If the serological response is not satisfactory, additional treatment should be given. The CDC guidelines recommend further intramuscular benzathine penicillin 2.4 million units on days 1, 8 and 15,[18] or a further course of procaine penicillin may be given over 10 to 14 days.

In late latent syphilis, the non-treponemal test may have been negative prior to treatment, and follow-up is usually not necessary. In the late forms of syphilis follow-up might be at 1, 3, 6, 12, 18 and 24 months with CSF examination at 24 months in patients with neurosyphilis. As the serological tests can remain positive for life (serofast) despite effective treatment, it is important to document this to prevent unnecessary retreatment. Follow-up in those co-infected with HIV has already been discussed in section 5.2.

8. Partner Notification

Partner notification should be discussed with all patients with syphilis. It is essential to try to tell partners at risk to fulfil ethical obligations to warn the unsuspecting, to assist in reducing disease burden and to identify networks hosting transmission. Because the incubation period of primary syphilis can be up to 90 days, sexual partners in the preceding 3 months should be notified. However, for patients with secondary syphilis, the interval back should be at least 1 year and with clinical relapse or in early latent syphilis, this ought to be extended up to 2 years. If a partner cannot attend regularly for examination and serological testing for exclusion of syphilis, immediate epidemiological treatment should be given.

9. Conclusion

Syphilis is an STI which is treatable to the point of presumptive cure. The mainstay of treatment is injectable penicillin, either as the benzathine or procaine salts. Treatments are efficacious but evidence for their use is based mainly on 50 years of clinical experience rather than controlled clinical trials. For the penicillin allergic, where other antibiotics have to be used, there is even less evidence of efficacy but doxycycline is the preferred alternative. Pilot studies with azithromycin have shown efficacy in incubating syphilis and a multicentre study is now underway in the US to assess the efficacy of a single oral dose of azithromycin 1g in patients with early infectious syphilis. Those with syphilis and HIV co-infection can be treated with the same regimen as is used for those without co-infection but a more prolonged follow-up is advisable.

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