Treatment of syphilis: the European view (paper nr 2)

R. Parkes, WHO Europe / MRC Programme on AIDS in Uganda / Liverpool School of Tropical Medicine, UK
P.C. van Voorst Vader, Dept of Dermatology, University Hospital, Groningen, The Netherlands

Introduction
The aim of this paper is to describe the current view regarding the treatment of syphilis in Europe. The method used is asking key-questions and giving answers to those questions, having reviewed the data available. The concept-paper including proposed answers to key questions was discussed in the IUSTI/WHO Europe Workshop Syphilis Management at the IUSTI Europe Conference on STI, October 7-9, 2004, 19 experts participating (IUSTI Europe: 13; WHO Europe: 6; USA: 1), in addition to 4 observers. Here the final version is given, after discussion in the workshop.

Recent general reviews on treatment:
2. Rompalo A. Treatment and prevention of syphilis in the HIV-infected patient. 2004; www.uptodate.com

Recent treatment guidelines

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1 Answers to key questions are based on proposed answers, which were discussed in the workshop.
Key question 1. Are the "basic assumptions" regarding treatment correct?

a) Is the division time of *T. pallidum* 30-33 hours and is the minimal treponemical level of penicillin 0.018 µg/ml?

The evidence from these comes from early experimental work, which was reviewed in a Bulletin of the WHO in 1972 and a WHO Scientific Group Report in 1982.[13,14] Both of these publications have been cited in many subsequent reviews. The assumption about division time is based on animal and in vitro laboratory tests performed between 1948 and 1950.[15,16] These stated that the duration of the treponemical level of the antimicrobial (penicillin) should be at least 7-10 days to cover a number of division times. Should a sub-treponemical interval of more than 24-30 hours occur, it was assumed that there will be a risk of multiplication of treponemes.

The theoretically assumed minimum treponemical serum penicillin (MBC) level of 0.018 µg/ml (0.03 IU/ml) is derived from the work of Eagle et al,[17] stating that *T. pallidum* is sensitive in vitro to ≥0.01 IU/ml penicillin. This level of 0.03 IU/m was said to provide a margin of safety and is maintained by various types of long-acting penicillin.[13,14] This minimum treponemical serum (MBC) level of 0.018 µg/ml is, however, substantially lower than the maximally effective in vitro level (0.36 µg/ml) described in these studies.[6] A single i.m. injection of 0.3 million units (MU) of benzathinepenicillin (BBP) produces a serum penicillin level of 0.03 IU/ml for about 7 days; the same dose of procaine penicillin in oil with aluminium monostearate (PAM) does so for 3-4 days. A single i.m. injection of 2.4 MU of BBP produces a serum level of ≥0.03 IU/ml for 21-23 days.[13,14]

In 1958 Nell reported, that a concentration of between 0.001-0.003µg/ml of penicillin was required to reduce mobility in a suspension of *T. pallidum* to 50% after 18 hours incubation.[18] In 1988 Norris and Edmonson, using in vitro cell culture, estimated a MIC of penicillin of 0.0005µg/l and a minimal bactericidal concentration of 0.0025µg/ml.[19] These later data do not refute the earlier data.

Although resistance of *T. pallidum* against penicillin has never been reported, recently however a genetic mutation of *T. pallidum* has been associated with resistance to macrolide antibiotics.[20] This is epidemiologically relevant, because syphilis at present is a widespread disease and because single-dose oral treatment with the macrolide antibiotic azithromycin has been advocated for syphilis-control programs.[21] This also raises the concern, that penicillin resistance may become an issue in the future. However, given that penicillin regimens are longer acting than single-dose macrolides, the long history of effective penicillin treatment and the small number of treatment failures with long acting penicillins, this currently seems unlikely.

Answer: It is not known whether the division time of *T. pallidum* still is 30-33 hours and whether the minimal treponemical level of penicillin should be 0.018 µg/ml, as established between 1948 and 1950. More recent data from 1988 do not refute this level of sensitivity of *T. pallidum* for penicillin. An area of concern is the recent report of macrolide resistance due to a genetic mutation of *T. pallidum*, which raises the question of penicillin resistance in *T. pallidum*.

It may be wise to try and verify the data surrounding division time and penicillin sensitivity. However, regardless of whether future research is performed regarding these items, clinicians should endeavour to establish the reason for clinical treatment failures in patients treated with penicillin.

b) Does *T. pallidum* divide more slowly in the late phase?

Latent syphilis has traditionally been divided into early and late stages, at either 1 year (CDC and European Guidelines)[8,12] or 2 years (UK and Russian Guidelines)[9,10,11,12] after infection. Active replication of *T. pallidum* (with a division time of 30-33 hours) is assumed in the early phase (primary and secondary syphilis as well as early latent syphilis) on clinical evidence. Rolfs in his review of 1993 states, that there is “limited animal model evidence” for the assumption, that *T. pallidum* divides more slowly in the late phase and therefore that longer exposure to penicillin is required.[6,22] However, this assumption is widely accepted.

In Rolfs’ opinion the major question regarding the management of late phase syphilis concerns the prevention of late disease, in particular the progression of asymptomatic neurosyphilis to symptomatic neurosyphilis.[4,6] Trying to find support for the concern, that one dose of 2.4 MU of BBP at day 1, 8 and 15 may not cure asymptomatic neurosyphilis (or prevent asymptomatic neurosyphilis from progressing to symptomatic neurosyphilis), he found one (flawed) study. This study reported, that the cumulative cerebrospinal fluid (CSF) relapse rate of asymptomatic neurosyphilis was 21% at 18 months in 47 patients treated with one dose of 2.4 MU of BBP, while it was 10% in a nonconcurrent comparison group of 53 patients treated with 4-5.9 MU of various other penicillin preparations.[6,23] A 1970-1979 study from Denmark, summarising the outcome of 16 cases of asymptomatic neurosyphilis, suggested, that various doses of PAM, procaine penicillin and even as
little as 4.8 MU of BBP were sufficient to minimise the risk of developing symptomatic neurosyphilis.[6,24] In conclusion: “The adequacy of three weekly i.m. injections of BBP for the treatment of (late) latent syphilis has never been adequately studied.”[4]

The persistence of *T. pallidum* after apparently effective treatment in late disease has been reported, giving support to the assumption of a longer division time in that stage, but the clinical significance thereof, if any, is not known.[5,7,25]

*Answer: There is limited animal model evidence for the assumption, that *T. pallidum* divides more slowly in the late phase of syphilis (>1-2 years after infection). The major issue regarding the management of late phase syphilis is assumed to be the prevention of late disease, in particular the progression of asymptomatic to symptomatic neurosyphilis. Although this risk is possibly decreased by treatment of longer duration than for early syphilis, as generally recommended, there is no adequate evidence for this.*

**Key question 2. Is benzathinebenzyl penicillin (BBP) 2.4 MU i.m. sufficiently effective in early syphilis?**

BBP is a long acting penicillin with treponemical serum levels still detectable 3-4 weeks after administration, as mentioned in the WHO reports from 1972 and 1982.[13,14] Akovyan et al confirmed these data and reported in 1998 the finding of a treponemical penicillin level (>0.018 µg/ml) for about 21-23 days (about 500 hours) after BBP (Extencillin®, manufactured in the Russian Federation) 2.4 MU i.m. in humans, with a similar pattern shown in mice.[26] Bicillin-1 (locally manufactured long acting penicillin) 2.4 MU gave this level for around 8 days (about 200 hours).[26]

However, subtreponemical penicillin serum levels have been reported within 21 days after single day treatment with 2.4 MU BBP i.m.: a) after 3 days (1/2 patients);[27] b) after 6-9 days (1/18 patients) and after 13-16 days (5/18 patients).[28]

The addition of lidocain as a diluent when administering BBP i.m. (e.g.: replace half or all of the solvent by lidocain 1% solution) reduces the pain of injection and it did not change penicillin levels in serum after 24 hours and in serum and urine after 28 days in 18 children aged 11-19 years.[29]

The question whether a single dose of BBP is effective in early syphilis is addressed in the review by Augenbraun and Rolfs, which was produced to discuss evidence for the CDC 1998 guidelines.[4] Their belief was, that this regime has been used effectively for a number of decades and Rolfs’ 1993 article reviewed 5 trials, which have shown it to be effective.[6] It should be noted, that this positive result is observed despite the fact, that asymptomatic cerebrospinal fluid (CSF) abnormalities, suggestive of asymptomatic neurosyphilis, were noted to occur in up to 20% of untreated early syphilis patients (24 patients with secondary syphilis and 23 patients with early latent syphilis acquired <24 months previously) in the pre-HIV era.[30] and in about the same range of frequency in 40 HIV-positive and HIV-negative patients with untreated primary and secondary syphilis.[31] Thus the host immune response (“spontaneous cure”) appears to be an essential element, as none of the parenteral treatment schedules consistently give treponemical CSF penicillin levels.[6,7]

However, in the UK the expert opinion has reservations about the effectiveness of BBP in early syphilis, given the UK experience with i.m. treatment of early syphilis on 10-14 consecutive days with procaine penicillin. A trial by Kapur et al showed serological failure being more common in seropositive patients with early syphilis treated with BBP than with procaine penicillin (12% vs. 5%).[32] Furthermore a subtreponemical penicillin serum level (<0.018 mg/l) has occasionally been found between 3 and 9 days after BBP 2.4 MU i.m.[27,28], possibly more likely to occur in younger patients, in whom the mean serum level appears to be lower than in older patients,[33] while 600.000 units of procaine penicillin daily appeared to give consistently adequate peak serum penicillin levels.[7] Further support in the argument against single dose BBP for early syphilis comes from a small number of case studies in immunocompetent patients, which revealed BBP failure as defined by the clinical response.[34,35] These rare clinical failures may be associated with the supposedly infrequent occurrence, mentioned above, of subtreponemical penicillin serum levels 3-9 days after BBP 2.4 MU i.m.[27,28] Treatment failures in early syphilis have been described more frequently in HIV-infected patients, where mainly serological failures, but also clinical failures (development of symptomatic neurosyphilis and ocular syphilis) have been described.[36-42] There is no general agreement however whether HIV infection significantly modifies the clinical response to therapy of early syphilis.[3,43] The latest review on syphilis and HIV infection, published in 2004, states that HIV-infected patients with early syphilis may have higher rates of treatment failure, adding that clinical failure is uncommon and serological failure is not.[2]
Both bodies of opinion in the USA and the UK recognize, that the early trials had limitations in terms of study design (e.g. non random patient allocation, differences in outcome criteria, small numbers of patients), which therefore makes comparisons between different treatments difficult.

In 1997 a prospective randomised, multicentre, double blind controlled trial to assess therapy in early syphilis was published. Rolfs et al studied 541 patients with early syphilis, including 101 who had HIV infection.[44] The patients were given either a single dose of BBP (2.4 MU i.m.) or this regime plus amoxycillin and probenecid (2g amoxycillin and 500mg probenecid orally 3x daily for 10 days). The trial showed, that there was an overall serologic relapse rate of 18% at six months in patients treated with one dose of BBP and 17% in the enhanced therapy group. In the primary stage the HIV-positive patients had a significantly higher risk of serologic failure than the HIV-negative patients and in secondary syphilis the risk was increased, but not significantly so. T. pallidum was found by PCR and/or rabbit-infectivity testing in the CSF of 32/131 patients at enrolment and in 7/35 after therapy, but no patient had clinical neurosyphilis. Note that only one patient (in the HIV positive group) had clinically defined treatment failure. Unfortunately the loss of follow-up was high (52% at one year). The absence of dramatic treatment failure in this trial and uncertainty surrounding the relevance of serologic failure with a normal clinical picture has lead to the continuation of the recommendation of this treatment (BBP 2.4 MU i.m. for early syphilis) in the American CDC syphilis guidelines of 1998 and 2002,[8] irrespective of HIV status.

In the Russian Federation syphilis guideline 1999 the recommendations are different from Western Europe and the USA (these Russian guidelines are incorporated as an appendix in the European syphilis guideline 2001 and the WHO Europe 2003 review on treatment of syphilis in Europe):[11,12] the recommended treatment with BBP for primary syphilis is 2.4 MU i.m. on day 1 and 8 and for secondary and early latent syphilis (<2 years previously acquired) 2.4 MU i.m. on day 1, 8 and 15. These recommendations are based on the assumption, that the duration of treatment should cover at least 10 division cycles (i.e. 330 hours=14 days) in the early phase and 20 cycles (660 hours=28 days) in the later phase.[26] For the late latent stage even longer courses are recommended.[12] Generally the duration of treatment in the Russian Federation is longer than advocated in Western Europe and the USA.

Despite the UK experience of acceptability of parenteral treatment,[44] there is concern over the refusal of patients to accept parenteral therapy. In one UK centre oral treatment rate was running at 30% in 2003. The UK early syphilis guideline 2002 recommends amoxycillin and probenecid for the treatment of patients, who refuse parenteral treatment, as this has well documented evidence for good biological availability,[46,47] although compliance with oral treatment is not assured. Therefore, the treatment choice appears to be between one single i.m. treatment dose with assured compliance but a seemingly small risk of failure versus a possibly more effective i.m. treatment on 10 consecutive days with a much greater risk of non-compliance.

For treatment of early syphilis in pregnant women, see paper nr 6: D. Mabey, “Prevention of congenital syphilis in Europe”. For serologic follow-up after treatment of early syphilis, see paper nr 3: P. French, “Serologic follow-up after treatment in Europe”.

Answer: Benzathine benzylpenicillin (BBP) 2.4 MU i.m. is sufficiently effective in early syphilis, despite the occurrence of cerebrospinal fluid (CSF) abnormalities suggestive of asymptomatic neurosyphilis in patients with secondary syphilis and early latent syphilis and the occasional occurrence of a subtreponemical serum penicillin level 3-9 days after treatment. In HIV-infected patients there may be a small risk of early complications (neurosyphilis, ocular syphilis), the consequence of which should be clinical and serologic follow-up during 1-2 years (follow-up is generally realized anyway at HIV-clinics) and instruction of the patient when to contact the physician.

Key question 3. Is BBP 2.4 MU im on day 1, 8 and 15 sufficiently effective in late latent syphilis and is there an indication for CSF examination in late latent HIV-infected syphilis patients before treatment?

As discussed in key question 1b, it is thought that late syphilis requires a longer course of treatment than early syphilis, as the treponemes may be dividing more slowly in the late latent stage of infection. Also, as discussed in key question 1b, the aim of treatment in late phase syphilis is assumed to be prevention of late clinically symptomatic disease, in particular the progression of asymptomatic to symptomatic neurosyphilis.[4,6] Therefore, although European and UK guidelines differ in terms of types of penicillin, there is a general consensus that the length of treatment for treatment of late syphilis should be 3-4 weeks, i.e. three doses separated by a week for BBP or 17-21 days for procaine penicillin and benzyl penicillin.
The UK late syphilis guideline 2002 recommends procaine penicillin as first choice, reflecting the clinical experience with only very few treatment failures over 50 years of procaine penicillin, which is corroborated by one published study, showing no clinical progression in 79 patients with late latent syphilis treated with procaine penicillin, although 22 were retreated due to serologic resistance.[10,48] The European syphilis guideline 2001 gives BBP, procaine penicillin and benzylpenicillin as options.[12]

Augenbraun and Rolfs stated in 1998: “The adequacy of three weekly i.m. injections of BBP for the treatment of (late) latent syphilis has never been adequately studied.”[4] However, they also reason, that: “In the final analysis, there is no indication from the literature that three weekly injections of BBP is inadequate for truly latent syphilis.”[4]

A 1970-1979 study from Denmark, summarising the outcome of 16 cases of asymptomatic neurosyphilis, suggested, that various doses of PAM, procaine penicillin and even as little as 4.8 MU of BBP were sufficient to minimise the risk of developing symptomatic neurosyphilis.[6,24] Musher et al also stated, that treatment of late latent disease prior to the HIV era revealed few cases of progression to symptomatic neurosyphilis.[39,43]

Regarding CSF examination in HIV-negative patients with late latent syphilis or latent syphilis of unknown duration the European syphilis guideline 2001 states:[12] “Lumbar puncture is an option in non-HIV-infected patients with late latent syphilis or in whom the duration of latent syphilis is unknown. This examination should exclude asymptomatic neurosyphilis, although the benefit may be marginal and the need minimal, as the risk of developing symptomatic neurosyphilis after standard parenteral treatment appears to be small in such patients.”

The European syphilis guideline 2001 recommends as indications for CSF examination:[12] a) Clinical evidence of neurosyphilis; b) Ocular, cardiovascular or gummatous syphilis; c) Concomitant HIV-infection (in late latent syphilis or latent syphilis of unknown duration). In syphilitic “sudden deafness” (auricular syphilis), which may occur, as ocular syphilis, as complication in early syphilis, sometimes as only symptom, the CSF is often normal, [7] but CSF examination should be considered.

The American CDC syphilis guideline 2002 recommends prompt CSF examination in patients with latent syphilis, who demonstrate any of the following criteria:[8] a) Neurologic or ocular signs or symptoms; b) Evidence of tertiary syphilis (e.g. aortitis, gumma, iritis); c) Treatment failure; d) HIV infection with late latent syphilis or syphilis of unknown duration.

Regarding treatment of late latent syphilis in HIV-infected patients with 3 weekly BBP injections Augenbraun and Rolfs state (1998): “Nor is there any indication that the regimen is inadequate, when the patient is concurrently infected with HIV and does not have asymptomatic neurosyphilis.”[4] The risk of patients with late latent syphilis or asymptomatic syphilis of unknown duration of having asymptomatic neurosyphilis appears to be increased in HIV-infected patients compared to non-HIV-infected patients, although controlled studies are lacking.[4,36-43,49-51] It is not generally accepted, that this should lead to standard CSF examination of asymptomatic HIV-infected patients with late latent syphilis or latent syphilis of unknown duration, because that strategy does not appear to be cost-effective and leads to finding CSF abnormalities (often present with concurrent HIV-infection!), which are difficult to interpret.[4,8,52,53] Moreover, CSF-abnormalities suggestive of asymptomatic neurosyphilis do not infrequently occur in early syphilis,[30,31] without generally accepted consequences for additional treatment or follow-up, thus interfering with the interpretation of CSF-examination in patients with latent syphilis of unknown duration (some of them may be early syphilis patients).

A practical problem is, that patients with late latent syphilis or latent syphilis of unknown duration may refuse CSF-examination or may default because of it. Priority should then be given to treatment, not to CSF-examination. Another option is to schedule CSF-examination later, during or just after the full treatment course. The consequence of demonstrating CSF-abnormalities consistent with asymptomatic neurosyphilis in patients with late latent syphilis or latent syphilis of unknown duration would be i.v. penicillin treatment, but it has not unequivocally been proven (and will be difficult to prove) that this approach is mandatory. The cost of i.v. treatment can be lowered by using the same strategy as for neuroborreliosis: start i.v. treatment in the clinic and continue and finish treatment on an out-clinic basis, if the regional care-organisation allows one to do so.

Rompalo states in her review of 2004 on syphilis and HIV, that CSF examination should be performed in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration.[2] Hard data to substantiate that recommendation are not given. The risk of asymptomatic neurosyphilis as diagnosed by a positive CSF VDRL test and elevated WBC count in CSF appears to be increased in HIV-infected patients with supposedly late latent syphilis or latent syphilis of unknown duration.[49-51] A serum RPR test titer ≥1:32 and a peripheral blood CD4+ cell count <350 cells/µl may help predict the likelihood of asymptomatic neurosyphilis and may thus aid in deciding to perform or
recommend CSF examination or not.\cite{2,51} The high RPR test titer as risk factor has been mildly questioned.\cite{6,54} In this situation a quantitative serum TPHA may help, as a serum TPHA titer <1:640 (which might be a TPPA titer of <1:640 or <1:1280) makes (asymptomatic) neurosyphilis unlikely, thus argues against CSF examination (see paper nr 5: B.L.Schmidt, "Laboratory diagnosis of neurosyphilis in Europe").

The question is, whether asymptomatic neurosyphilis in late latent syphilis (patients with latent syphilis of unknown duration may in fact have early latent syphilis, with CSF-abnormalities which may occur at that stage, which apparently do not have consequences,\cite{30,31} given the general experience) results in a risk, despite standard treatment with BBP i.m., of subsequent development of symptomatic neurosyphilis of such magnitude, that standard CSF examination should be recommended (see paper nr 4, M. Janier: "Syphilis and HIV-infection: the European view"). If CSF examination is not performed, an alternative option is clinical and serologic follow-up of these patients, as is generally performed routinely in HIV-positive patients, and instruction of the patient when to contact the physician.

In the review of Rompalo it is also stated, that pharmacological data suggest that an interval of 10-14 days between doses of BBP may be acceptable.\cite{2} One may even wonder, why in the BBP treatment series of day 1-8-15 for late latent syphilis day 8 is included, given the pharmacokinetic data.\cite{13,14,26} The statement of Rompalo is supported by the findings of Idsoe and Akov,\cite{13,26} but does not agree with the findings of Frenz et al and Polnikorn et al,\cite{27,28} as also reviewed by Goldmeier and Hay,\cite{7} reporting that subtreponemicidal penicillin serum levels may occur 3-9 days after BBP 2.4 MU i.m.

As patients with symptomatic ocular or auricular syphilis (without other symptoms of CNS involvement) are generally treated with i.v. penicillin to ensure optimal tissue penetration, it is not essential to perform CSF examination in these patients, which may demonstrate CSF abnormalities consistent with neurosyphilis (more frequent in ocular than in auricular syphilis),\cite{26,8} as concomitant CSF abnormalities, if present, are treated concurrently.

For treatment of late latent syphilis in pregnant women, see paper nr 6: D. Mabey, "Prevention of congenital syphilis in Europe". For serologic follow-up after treatment of late latent syphilis, see paper nr 3: P. French, "Serologic follow-up after treatment in Europe".

Answer: The evidence for the need to increase the duration of treatment in late latent syphilis as compared to the duration of treatment for early syphilis is inadequate. BBP 2.4 MU im on day 1, 8 and 15 appears to be sufficiently effective in late latent syphilis, but again the evidence for this is inadequate.

European 2001 and American 2002 syphilis guidelines recommend CSF examination before treatment in HIV-infected patients with late latent syphilis or latent syphilis of unknown duration. A serum TPHA titer <1:640, RPR test titer ≥1:32 and a peripheral blood CD4+ cell count <350 cells/µl may help predict the likelihood of asymptomatic neurosyphilis and may thus aid in deciding to perform or recommend CSF examination or not. There are no hard data, however, that the risk of developing symptomatic neurosyphilis from asymptomatic neurosyphilis after the above mentioned standard treatment is of such magnitude in HIV-infected patients, that CSF-examination is mandatory. This risk appears to be small indeed in HIV-negative patients.

If HIV-infected patients with late latent syphilis or latent syphilis of unknown duration refuse CSF-examination, priority should be given to treatment, not to CSF-examination. If CSF examination is not performed, an alternative option is clinical and serologic follow-up of these patients, which is generally routinely performed in HIV-infected patients, and instruction of the patient when to contact the physician.

It may be prudent to re-investigate the pharmacokinetic properties of BBP to check for the need of a dosage of BBP on day 1, 8 and 15.

Key question 4. Penicillin allergy: what are the alternatives?

Regarding treatment of syphilis with other antibiotics than penicillin the published data are limited. There has been less clinical experience with their usage than with penicillin. Evidence from biological and animal studies contributes to confidence in their efficacy. This has been discussed in review articles.\cite{6,7} Regarding penicillin allergy: a patient history, which does or may suggest anaphylaxis, is a much more serious and relevant issue than a history of a rash. However, a history of a rash does not exclude anaphylaxis. Reliable differentiation between anaphylaxis and a non-anaphylactic reaction ("rash") may require penicillin allergy tests.

The main oral alternatives are doxycycline, tetracycline, erythromycin and azithromycin. Concerns with oral therapy are the possible lack of bioavailibility, especially with erythromycin and...
azitromycin, as these macrolides do not adequately cross either the blood brain barrier or the placenta,[25,55] issues regarding compliance and the development of resistance against macrolides (erythromycin and azithromycin).[20,56]

The evidence for doxycycline comes from 2 small non-randomised studies. Harshan et al., giving 100 mg once daily, studied 40 patients with early syphilis, only 20 of which completed treatment, while 7 were followed up with low titres at 3 years.[57] Another study by Onada followed 51 patients with all stages of syphilis. There was a good serologic response after repeated treatment courses of 28 days with doxycycline 100 mg twice daily in 100% of those with primary syphilis, decreasing to 68% with late latent syphilis.[58] Unfortunately clinical relapse rates were not published in that article. Failure of doxycycline treatment of HIV-positive patients with secondary syphilis has been observed (personal observation; see paper nr 4, M. Janier: “Syphilis and HIV-infection, the European view”). One patient with treatment failure has been described in the literature, according to our knowledge anno 2004: ten months after diagnosis of early latent syphilis and two courses of doxycycline (given because of penicillin allergy) no serologic response was found (serologic failure) and asymptomatic neuropsilosis was demonstrated.[59] It seems that clinical experience with doxycycline rather than evidence has established it as the first choice treatment option in penicillin allergy.

Azithromycin has comparable efficacy as doxycycline in the small number of clinical trials performed. A review article in 2001 by Augenbraun on behalf of the CDC has placed greater emphasis on the role of azithromycin in the treatment of syphilis.[3] In vitro and animal models suggested, that azithromycin would be effective against syphilis, which was confirmed by clinical studies in patients with early syphilis.[1,3,20] In 2002 a trial was published on clinical efficacy in early syphilis (primary and secondary stage) with azithromycin administered as a single 2 gram dose or as two 2 gram doses given one week apart.[60] On the basis of the available evidence the CDC review paper of 2001 suggests, that azithromycin 1-2 gram given in a single dose may be appropriate in primary and secondary syphilis, as was suggested in the American CDC syphilis guideline 2002.[3,8] However, a paper published in 2004 reported azithromycin resistance of T. pallidum in an American HIV-infected patient with primary syphilis. A mutation (associated with macrolide resistance) was identified in T. pallidum derived from this patient. Functional azithromycin resistance in vivo was confirmed. A high frequency of this mutation in T. pallidum was demonstrated in samples from four geographically diverse sites in the USA and Ireland (San Francisco, Seattle, Baltimore and Dublin).[20] The frequency of the presence of the mutation appears to have increased over recent years (4% in 1999-2002, 37% in 2003). In 2000 another report also identified a macrolide (erythromycin and azithromycin) resistant strain of T. pallidum isolated already in 1988 from a patient with secondary syphilis.[56] Azitromycin, like other macrolide antibiotics, has limited placental transfer.[55]

Parenteral ceftriaxone is mentioned in all guidelines and there have been some papers showing efficacy in treating early syphilis and neurosyphilis.[3] Regarding early syphilis there have been 4 randomised trials comparing ceftriaxone and BBP.[61-64] These had between 21-36 patients and there was only one retreatment in a patient, who received a single dose of 3 gram of ceftriaxone. It is unclear if this was reinfection or clinical failure. The use of ceftriaxone has also been investigated in latent syphilis in HIV-infected patients, where it was associated with a comparatively high rate of serologic non-response and serologic relapse, but this also occurred in the control group treated with procaine penicillin.[37] Clinically symptomatic syphilis did not develop during this study. Another trial showed that out of 56 HIV-infected patients with late latent syphilis and neurosyphilis, randomised to ceftriaxone or BBP, there were 2 clinical relapses in the BBP group and 1 in the ceftriaxone group, although the serologic response was only around 65% in both.[65] Several other studies have appeared using ceftriaxone for latent syphilis or neurosyphilis in HIV-infected patients.[43]

The ceftriaxone dosage recommended in the various guidelines for early syphilis varies: a) American CDC syphilis guideline 2002: 1 gram i.m. or i.v. daily for 8-10 days;[8] b) European syphilis guideline 2001: 250-500 mg daily i.m. for 10 days;[12] c) UK early syphilis guideline 2002: 500 mg i.m. daily for 10 days;[9] d) Russian Federation syphilis guideline 1999: 250 mg i.m. daily for 5-10 days for primary syphilis, 500 mg i.v. daily for 14 days for secondary and early latent syphilis.[12]

Data are insufficient to be sure about safety of use of ceftriaxone during pregnancy. A survey of infectious disease specialists in the USA found, that ceftriaxone was commonly used as an alternative for penicillin.[3]

Anaphylaxis to penicillin is regarded as a contraindication for the use of a cephalosporins, which includes the third generation drug ceftriaxone. One should consider allergy tests, including a penicillin-specific IgE test, to exclude anaphylaxis before starting ceftriaxone i.m. or i.v., if the history suggests an anaphylactic reaction to penicillin.[8,9,10]
For early syphilis in patients with penicillin allergy the American CDC syphilis guideline 2002 recommends the following treatment options during 14 days in preferred order of use: doxycycline (100 mg 2x daily), tetracycline, ceftriaxone and azithromycin.[8] The UK early syphilis guideline 2002 has removed tetracycline due to widespread availability of doxycycline, but includes erythromycin.[9] The European syphilis guideline 2001 incorporates all treatment options mentioned for early syphilis. Regarding alternative treatment options for patients with penicillin allergy the German syphilis guideline 2001 differs from the American CDC syphilis guideline 2002 by avoiding ceftriaxone and azithromycin due to lack of evidence.[66] The Russian Federation syphilis guideline 1999 suggests doxycycline, tetracycline, ceftriaxone and azithromycin.[11,12]

For late latent syphilis or latent syphilis of unknown duration in patients with a penicillin allergy doxycycline (for 21-28 days) is recommended by the American, UK and European guidelines as first choice treatment option in case of penicillin allergy.[8,10,12] The American 2002 and European 2001 guidelines recommend 100 mg 2x daily for 21-28 days.[8,12] The UK 2002 guideline recommends 200 mg 2x daily for 28 days, as it allows for better therapeutic safety if doses are missed.[10] This dose of 2x 200 mg doxycycline daily is also recommended for neurosyphilis, as it appears to give a treponemical CSF level.[12,67] The American 2002 and European 2001 guidelines have tetracycline as second choice treatment option. The European 2001 guideline lists erythromycin as third choice treatment option, despite concerns about inadequate placental transfer. Azithromycin is avoided in late syphilis. In the Russian Federation syphilis guideline 1999 ceftriaxone is the only alternative for penicillin for the indications late latent and neurosyphilis (dosage: 1-2 gram daily i.m. for 14 days).[11,12]

Penicillin desensitization, which is easy to perform (within a few hours, after which treatment can be given, all on the same day), after allergy tests have given proof of anaphylaxis for penicillin (test material can be difficult to obtain), is an important option. For both penicillin allergy tests and desensitization a protocol is given in the American CDC syphilis guideline 2002 and UK late syphilis guideline 2002.[8,10] If anaphylaxis is excluded, some experts do give penicillin, supervised, plus antihistamine medication (because of the history of a rash). Penicillin desensitization is recommended in the American CDC syphilis guideline 2002 and UK early syphilis guideline 2002 for pregnant women with syphilis (early and late) with penicillin anaphylaxis (see also paper nr 6, D. Mabey: “Prevention of congenital syphilis in Europe”)[8,9] and is an option for HIV-infected individuals with syphilis (possibly especially for patients with late latent syphilis or latent syphilis of unknown duration) and penicillin anaphylaxis (see paper nr 4, M. Janier: “Syphilis and HIV-infection: the European view”).

Answer: Guidelines suggest, that the preferred treatment option for both early and late syphilis patients with or suspected of penicillin allergy is doxycycline, but there is little published evidence for this. If doxycycline is used for late latent syphilis or latent syphilis of unknown duration, the dosage should be higher and of longer duration (2x 200 or 400 mg daily, 21-28 days) than in early syphilis (2x100 mg daily for 10-14 days). Ceftriaxone (early syphilis: 500-1000 mg daily, 8-10 days, i.m.; late latent syphilis or neurosyphilis: 1 gram daily, 15 days, i.m.) has more evidence to support its use, but the evidence is still limited. Anaphylaxis for penicillin is regarded as a contraindication for the use of ceftriaxone. Azithromycin use for early syphilis became more widespread in recent years, but macrolide resistance of T. pallidum has been demonstrated, apparently occurring fairly frequently.

An important and simple option, easy to perform, is penicillin desensitization (after allergy tests), for which protocols are given in the American CDC syphilis guideline 2002 and the UK late syphilis guideline 2002. Desensitization of patients with penicillin anaphylaxis appears to be the preferential option for pregnant women (with early and late syphilis) and should be considered for non-pregnant patients, possibly especially for HIV-infected individuals with late latent syphilis or latent syphilis of unknown duration and anaphylaxis for penicillin.

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