Review of Current Evidence and Comparison of Guidelines for Effective Syphilis Treatment in Europe

ABSTRACT

The purpose of this review is to compare the differences in treatment regimens for syphilis in the European region. There is still a lack of evidence and consensus on the most appropriate regimes for different stages of the infection. The review outlines the evidence and current thought that supports these differences, by consolidating information summarised in the guidelines and in the many review articles addressing the management of syphilis. The background section presents an overview of why differences in treatment recommendations exist. The body of the paper compares recommended treatments for different stages of disease and clinical contexts. Recommendations from the different guidelines are presented together in tabular form to facilitate comparison, and the appendices refer to the full texts of the guidelines discussed. With the advent of HIV infection and the increased levels of syphilis in many geographical regions, the need for effective treatment and harmonized treatment guidelines is greater than before.

Keywords

SYPHILIS – prevention and control
GUIDELINES
COMPARATIVE ANALYSIS
META-ANALYSIS
EUROPE

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Foreword

"Come now, what regimen, what cure must be adopted to combat this great plague and what is appropriate at which stage of the illness I shall disclose and I shall expound the wonderful discoveries of men."

Girolamo Frascastoro's Syphilis 1530 *(1)*

This technical document reviews and compares syphilis treatment guidelines from Europe, the United Kingdom, the United States and Russian Federation. The guidelines and recommended treatment regimens differ somewhat from one guideline to another even though they are largely drawn from the same evidence.

The Russian Federation guidelines, however, differ considerably from the other three guidelines in that they are based more on Russian experience and locally manufactured penicillin formulations; where they recommend imported drugs, the recommended doses or duration of therapy tend to exceed those in the other guidelines. The difference between guidelines from Russian Federation and those from elsewhere is explained, in part, by the "historical aspect" of syphilis management in this region.

Syphilis management in Russian Federation has been of special "interest" to many physicians, almost mythical to others. Changes in policies for syphilis management are still ongoing in the Commonwealth of Independent States (e.g. inpatient versus outpatient management; dermatovenereologists versus primary health care concepts; locally manufactured drugs versus imported ones; cost and quality aspects, etc.). Future guidelines will undoubtedly show further evolution of thinking surrounding these and other issues.

Treatment of syphilis has always been complex and confusing, having come with different recommendations in different guidelines for many years. There are areas of treatment where more data are needed. These areas need to be clearly identified so that appropriate research priorities can be defined and feasibility of such research established.

There is an obvious need to harmonize syphilis treatment guidelines not only in Europe but globally, and this review contributes to the beginning of such a process.

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Introduction

Ever since syphilis was first described its treatment has caused controversy. Despite Frascatoro's claim the first effective cure for syphilis (*Treponema pallidum subsp pallidum*) was penicillin, which became available in the 1940s. Internationally there is now a broad consensus about the most effective therapies for syphilis. However, differences still remain around many details of treatment and the evidence base is not complete. In an attempt to rationalize treatment strategies, guidelines are regularly produced by different countries, regions and by the WHO worldwide. European guidelines were recently elaborated as a consensus document based on the Austrian, Dutch, German, Russian Federation and United Kingdom national guidelines; they were approved by the European branch of the International Union against Sexually Transmitted Infections (IUSTI) and the Regional Office for Europe of the World Health Organization *(2)*.

The purpose of this paper is to compare the most recent European *(2)*, United Kingdom *(3,4)*, and Russian Federation *(6)* guidelines, to include the CDC guidelines *(5)* and to highlight differences in recommended treatments between them. The paper outlines the evidence and current thought that supports these differences, by consolidating information summarised in the guidelines and the many excellent review articles addressing the management of syphilis. The background section presents an overview of why differences in treatment recommendations exist. The body of the paper compares recommended treatments for different stages of disease and clinical contexts. Recommendations from the different guidelines have been presented together in tabular form to facilitate comparison, and the appendices refer to the full texts of the guidelines discussed.

While precise definitions of the different stages of syphilis infection are somewhat arbitrary and have always varied, a detailed discussion of this is beyond the remit of this paper. Where the different guidelines use different definitions for stage of infection these are noted but the treatment of each stage of syphilis is presented as defined by the individual guidelines. For information on the diagnostic criteria for each stage of disease the reader should refer to the original guidelines.

Background

In his 1993 review article (which reviews the evidence base for the recommendations for the management of syphilis presented in the US Centers for Disease Control (CDC) Sexually Transmitted Disease Guidelines), Robert Rolfs concludes, "the evidence upon which recommendations for syphilis therapy are based remains inadequate for such a complicated disease. It is surprising that treatment has been as successful as it has, given the poor data and simplistic approach followed for the last 40 years" *(7)*. This lack of evidence stems from a number of factors, which together have led to a paucity of good clinical trials.

Firstly, there is incomplete understanding of the natural history and pathogenesis of the disease, which is compounded by the inability to culture the organism in vitro. This makes treatment outcomes difficult to measure, necessitates long-term serological follow up and constrains the interpretation of uncontrolled studies. Secondly, the diagnostic criteria for different stages of disease are complex, and to some extent arbitrary, creating difficulties for both the application of study inclusion criteria, and for the conduct of satisfactory meta-analyses. Thirdly, a significant decline in many countries, in the occurrence of syphilis since the advent of penicillin *(8)* has made recruitment of sufficient cases to adequately power single centre trials very difficult. In

addition there is a lack of incentive (given low costs of treatment) for pharmaceutical companies to support syphilis treatment research. In combination these factors create considerable practical difficulties in resourcing and executing definitive clinical trials.

In assessing and interpreting those clinical trials which have been carried out, we are faced with a few areas of uncertainty that must be considered. In particular, the relationship between serological response, clinical response, and the persistence of potentially pathogenic organisms is complex. Syphilis serology is difficult to interpret, for example treponemal tests usually remain positive even after successful treatment, and non-treponemal tests (e.g. RPR, VDRL) can be influenced by other biological factors. Also it is unlikely that the infection is ever completely cleared *(9)*, therefore the clinical picture is of utmost importance. This compounds the difficulty in assessing response to antibiotics, and increases the need for long-term follow up in clinical studies. Unfortunately none of the studies reviewed have achieved a long-term follow up. Moreover the role of the host immune response needs to be considered assessing clinical outcomes to the infection, as 60% of untreated patients do not develop long-term complications *(10)*.

Discrepancies between treatment guidelines recommended for different regions are clearly influenced by the lack of evidence from clinical research. However, these are also determined by different clinical traditions, and by historical and geographical variation in volumes of clinical experience and levels of clinical expertise with different regimes. Regions also differ with respect to the acceptability of different regimes within their culture (i.e. a propensity to either oral or parenteral treatment) and to the local availability of medicines. These issues are particularly pertinent for the understanding of Russian Federation guidelines. In the Russian Federation during the Soviet years there was obligatory adherence by physicians to the government guidelines. These were based solely on USSR data, with very rare consideration to international research *(6)*. However, this report shows that even the CDC and United Kingdom guidelines come to different conclusions about the most efficacious treatment, despite the fact that both refer to the same body of English language literature.

Despite these discrepancies, there is an international consensus supporting the use of parenteral penicillin for first line management of all types of syphilis infection. The rationale for penicillin use is its treponemicidal action. This was demonstrated by reports that, in vitro, a reduction of 50% in the mobility of a suspension of *T. pallidum* occurred following 18 hours incubation with concentrations of between 0.001–0.003 μg/ml of penicillin *(11)*. In cell culture the minimal inhibitory concentration (MIC) of penicillin has been estimated at 0.0005μg/ml, and the minimal bactericidal concentration (MBC) at 0.0025 μg/ml *(12)*. In vitro studies on rabbit serum estimated that 0.005–0.01 μg/ml of penicillin gives clearance of treponemes *(13)*. WHO has therefore recommended that regimes should achieve serum levels of >0.018 μg/ml penicillin in order to maximize success in treatment *(14)*. The question of whether a treponemicidal level of penicillin in the CSF needs to be achieved in all stages of disease is controversial and is further discussed below.

Because of the long treponemal division time (30–33 hours) *(15)* treatment regimes need to achieve high serum concentrations of agent over extended periods. Moreover, because *T. pallidum* infects the central nervous system and may also infect the fetus of an infected woman, adequate penetration of blood–brain and placental barriers needs to be achieved in the treatment of some patients. These factors explain the rationale for recommendations of different treatment regimes in different stages of infection and for the management of infected pregnant women. In

recent years reports of patients with human immunodeficiency virus (HIV) contracting syphilis has led to concern over whether current regimes are sufficient in immunocompromised individuals. These issues are addressed in this paper, where relevant to the stage of disease.

Parenteral treatment is generally the treatment of choice since it delivers higher serum levels than oral treatment. It has the added advantage that the treatment is, by definition, directly observed. The main discrepancies between guidelines are, therefore, between the *types* of penicillin used (i.e. penicillins with a different length of action and CNS/placental penetration), the *dose* and the *duration* of treatment course. There are three main types of penicillin: benzyl penicillin sodium, which is short acting and is given every six hours (qds), intermediate length procaine benzyl penicillin (PBP) given daily (od), and long acting benzathine benzyl penicillin (BBP) given once weekly (ow). Table 1 summarizes the different types of penicillin mentioned in the guidelines. Other differences occur between alternative regimes for patients with penicillin allergy and those who refuse parenteral treatment.

In what follows we review and compare the European, United Kingdom, CDC and Russian Federation guidelines for the management of syphilis; German guidelines have also been addressed *(16)*. These are very similar to the CDC guidelines, but when differences occur they are described in the text. We present the review according to the following categories of syphilis cases: early syphilis; uncomplicated late latent/cardiovascular/gummatous syphilis; neurosyphilis; syphilis with HIV infection; syphilis in pregnancy; congenital syphilis; and the epidemiological treatment of contacts.

Early Syphilis

Early syphilis (Table 2) is defined as the primary, secondary and early latent stages of syphilis. In CDC and European guidelines early latent is defined as syphilis acquired <1 year previously and in the United Kingdom and Russian Federation ones <2 years previously. In view of the treponeme division time discussed above treatment duration of at least seven days is recommended for early syphilis *(14)*. CDC guidelines recommend only benzathine penicillin (BBP), (one dose of 2.4 million units IM). The United Kingdom guidelines differ by proposing Procaine penicillin (PBP) (750 mg IM for 10 days) as first line therapy. BBP is an alternative treatment in the United Kingdom guidelines, with either one dose, or two doses separated by one week. The first line treatment in the European guidelines is also BBP; PBP is second line in the European guidelines, which also include benzyl penicillin.

BBP is a long acting penicillin with serum levels still detectable four weeks after administration *(17)*. The question of whether a single dose of BBP is effective is addressed in the review by Augenbraun and Rolfs, which was produced to discuss evidence for the CDC 1998 guidelines *(18)*. Their belief was that this regime has been used effectively for a number of decades, and Rolfs' 1995 article reviewed five trials which have shown it to be effective *(7)*. However, in the United Kingdom the expert opinion has reservations about the effectiveness of BBP in some clinical trials. A trial by Smith et al. showed comparable results between BBP and PBP in early syphilis *(19)*; however, in asymptomatic neurosyphilis there was a 21% CSF relapse rate with BBP, which was twice that of other penicillins. Another trial by Kapur et al. showed serological failure being more common in seropositive early syphilis in patients treated with BBP compared with PBP (12% compared with 5% respectively) *(20)*. Both bodies of opinion recognize that these early trials had limitations in terms of study design (e.g. non-random patient allocation,

differences in outcome criteria, small numbers of patients), therefore making comparisons between different treatments difficult.

Since 1993 there has been one prospective randomized, multicentre, double blind controlled trial to assess therapy in early syphilis. Rolfs et al. studied 541 patients with early syphilis, including 101 who had HIV infection *(21)*. The patients were given either a single dose of BBP (2.4 million units IM) or this regime plus amoxycillin and probenecid (2 g amoxycillin and 500 mg probenecid orally 3 x day for 10 days). The trial showed that there was an overall serological 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 of syphilis the HIV positive patients had a higher level of serological failure than the HIV negative patients, but in secondary syphilis there was no statistical difference. *T pallidum* was found in the CSF of 32/131 patients at enrolment and 7 out of 35 after therapy, but no patients had clinical neurosyphilis. One patient (in the HIV positive group) had clinically defined treatment failure. Unfortunately the loss to follow up was high (52% at one year). The absence of dramatic treatment failure in this trial, and uncertainty surrounding the relevance of serological failure with a normal clinical picture has led to the continuation of this treatment in the CDC guidelines, irrespective of HIV status *(18)*.

In support of the argument against single dose BBP, small numbers of case studies have revealed BBP failure in pregnant women *(22–25)*, immunocompetent patients *(26,27)* and HIV positive patients *(28–34)*. This has led to the United Kingdom guidelines recommending BBP as an alternative, but with a second dose one week after the first, to consolidate treatment. Work by Fiumara on this regime showed complete serological response at one year in early and at two years in secondary syphilis (with the exclusion of some patients thought to have been reinfected) *(35)*. In combination, this clinical evidence is simultaneously used to support use of single dose BBP in the United States and highlight anxieties over its use in the United Kingdom. This illustrates the differences in interpretation of results of studies by different clinicians, which then influence the recommendations for use of different preparations.

The use of PBP as a first line by the United Kingdom is supported by evidence from several reports showing good clinical results *(9,21,36,37)*. Elliot showed use of procaine penicillin 4.3–15g in 381 patients, with a mean cumulative retreatment rate over 11 years of <1% (range 0–4%) *(38)*, Brown et al. showed in patients treated with 750 mg PBP daily for 8 days a retreatment rate of 3.8% at 12 months *(39)*. The use of daily IM injections of PBP has been shown to be acceptable by patients *(40)*.

German guidelines propose the use of PBP as first line therapy (1 million units od IM for 14 days), with BBP as an alternative (2.4 million units IM single dose). In 1985 IV Benzyl penicillin in very high doses over a short period of time was compared with 30 days of PBP. The regimes compared a total of 120 million units Benzyl penicillin over 36 hours (60 million units IV infused over 12 hours, with a break of 12 hours, and then repeated with 60 million units infusion over 12 hours) with PBP (1 million units IM daily for 30 days).The study included 104 patients with early syphilis or reinfection, and showed no difference in achieving a four-fold decrease in VDRL titre within one year. However, this regime was not studied further and was not generally accepted *(41)*.

Russian Federation guidelines are more diverse incorporating many types of penicillin of various lengths of action. This may be explained by the historical influences mentioned above; in particular the availability of locally produced penicillins and non-availability of products

produced abroad. Long acting preparations of penicillin have been manufactured in USSR in the form of bicillin-1 and bicillin-3 since 1962, but these were used in combination with other treatments (e.g. bismuth, arsenic and soluble penicillin) *(6)*. Bismuth and arsenic ceased to be used by 1988, and foreign preparations of long acting penicillin (i.e. BBP) have only been available since 1995.

In Russian Federation primary syphilis is treated with shorter courses of penicillin than secondary and early latent stages. Currently there is no weighting of the different treatments, but a first line therapy will be recommended in the future *(42)*. For primary syphilis BBP is given in a regime of 2 doses of 2.4 million units, separated by 7 days. Three doses of BBP are given at weekly intervals in secondary or early latent syphilis. Benzyl penicillin is used in the same way as in the European guidelines, and administered for 10 days in primary syphilis and 20 days in secondary or early latent. In primary syphilis PBP is recommended at either the United Kingdom standard dose of 600 000 units or doubled; duration 10 days in primary and 20 days in secondary or early latent. Novocaine benzyl penicillin (NBP) is the local alternative to PBP, but is administered twice a day. Locally manufactured Bicillin-3 and Bicillin-5 are also included.

In the review paper by Akovbian and Filatova *(6)* there are citations of treatment results of both benzyl penicillin and benzathine penicillin treatments. This review cites five articles on the efficacy of benzathine treatment with between 341 and 3132 patients. Another researcher performed a retrospective analysis (controlled for age, sex, stage of disease, accompanying diseases and compliance with treatment/follow up) comparing treatment of 812 patients with early syphilis. Patients had received either benzathine penicillin or benzyl penicillin. Patients with primary syphilis received 15 days treatment, secondary/early latent received 28 days treatment. This showed no difference between the two groups with primary or secondary syphilis. However, there were 13/406 failures of benzyl penicillin and 32/406 cases of failure with BBP in early latent syphilis >6 months duration *(43,44)*.

For treatments other than penicillin the evidence base is thinner and there has been less clinical experience in their usage as many of the antibiotics are newer. Table 7 outlines the different reported clinical trials which have sought to evaluate these therapies *(50–53,81–83,109–114)*. Evidence from biological and animal studies also contributes some confidence in their efficacy, and these have been discussed in the previous review articles *(7,9)*. The main oral alternatives are doxycycline, erythromycin, azithromycin and tetracycline. The main concerns with oral therapies are possible lack of bio-availability (especially with erythromycin as this doesn't cross either the blood–brain barrier or the placenta) *(45,46)* and issues surrounding compliance.

Azithromycin has comparable efficacy to doxycycline in the small number of clinical trials performed. The recent review article by Augenbraun for the CDC has placed greater emphasis on the role of azithromycin in the treatment of syphilis *(47)*. In vitro and animal models *(48,49)* suggested that azithromycin would be effective against syphilis, but there have also been recent trials on clinical efficacy. Table 7 summarizes the trials cited in this paper *(50–53)*. On the basis of this evidence this latest CDC review paper suggests that azithromycin 1–2 g single dose may be appropriate in primary and secondary syphilis. There has been one report of a macrolide resistant strain of *Treponema pallidum* isolated from a patient with secondary syphilis *(54)*. Parenteral ceftriaxone is mentioned in all of the guidelines, and the Augenbraun review suggests that although there is minimal evidence for its use, there have been some recent papers showing efficacy in treating early syphilis and neurosyphilis (see Table 7). A survey of infectious disease specialists in the United States found that it was commonly used as an alternative *(47)*.

The CDC guidelines cite the following treatments in order of use; doxycycline, tetracycline, ceftriaxone and azithromycin. The United Kingdom guidelines have removed tetracycline due to widespread availability of doxycycline *(3)*, but include erythromycin. Despite the United Kingdom experience of acceptability of parenteral treatment *(40)* there is concern over the refusal of patients to accept parenteral therapy and in some centres the oral treatment rate is running now at 30% *(55)*. The United Kingdom guidelines recommend amoxycillin and probenecid for the treatment of patients who refuse parenteral treatment, as this has well documented evidence for good biological availability *(55,57)*. European guidelines incorporate all the therapies mentioned above. It is with alternative therapies that the German guidelines differ from the CDC guidelines, by avoiding ceftriaxone and azithromycin due to lack of evidence. Russian Federation guidelines suggest doxycycline, tetracycline, ceftriaxone and azithromycin, with oxacillin and ampicillin cited as alternatives to long acting penicillins. There is one Russian Federation study that showed in 65 patients a good response with ceftriaxone *(6)* (see Annex 5).

Uncomplicated Late Latent/Cardiovascular/Gummatous Syphilis

There is variation in the definitions of late latent syphilis in different guidelines; the CDC and European guidelines use a period of >1 year since infection, while United Kingdom and Russian Federation guidelines use a period of >2 years since infection to define late latent disease. This needs to be taken into account when considering and interpreting discrepancies.

It is thought that late syphilis requires a longer course of treatment than early syphilis as the treponemes may be dividing very slowly in the late latent stage of infection, as evidenced by both animal studies and some case reports of treatment failure *(58–62)*. Therefore, although the guidelines differ in terms of types of penicillin there is a consensus that the length of treatment should last 3–4 weeks. (That is three doses each separated by a week for BBP, or 17–21 days for PBP and benzyl penicillin.)

Prior to HIV infections the treatment of late latent disease with three doses of BBP revealed few cases of progression to neurosyphilis *(63)*. CDC guidelines have BBP as the only recommended regime for late syphilis, as discussed by Augenbraun and Rolfs *(18)*. Although this review could find no definitive evidence for the efficacy of BBP in late latent syphilis, neither did it find any evidence to the contrary. In contrast the United Kingdom and European guidelines recommend PBP regimes, as well as BBP regimes, reflecting the clinical experience of only very few treatment failures over 50 years with PBP *(3)*. This clinical experience is supported by a study by Hellerstrom and Skog using PBP in 79 patients with uncomplicated late latent syphilis, which showed a good response or no change in serology with no clinical progressions *(64)*. The European Guidelines also include benzyl penicillin regimes, as well as BBP and PBP.

The Russian Federation guidelines reflect concern drawn from literature published in Russian journals about treatment failures with BBP in early latent syphilis as discussed above *(43,44)*. Therefore, the Russian Federation guidelines do not propose the use of BBP in late latent syphilis. First line treatment in Russian Federation is benzyl penicillin qds as an inpatient regime with a 28-day course followed by 14 day break then repeat 14-day course. NBP and PBP are alternatives. The use of a treatment interruption may be due to the historical use of toxic agents such as arsenic and bismuth, which required interrupted therapy.

For penicillin allergy, doxycycline is cited by CDC, United Kingdom and European guidelines as first line therapy. CDC proposes use of 100 mg bd for 28 days, the United Kingdom guidelines suggest that 200 mg bd for 28 days is preferable, and European guidelines suggest 200 mg daily for 21–28 days. CDC and European guidelines have tetracycline as second line. European guidelines support erythromycin as third line despite concerns around placental transfer. The United Kingdom guidelines have amoxycillin and probenecid as the second line therapy, as efficacy has been shown in neurosyphilis *(65)*.

Worldwide, azithromycin is avoided in late syphilis. Russian Federation proposes ceftriaxone only, based on published data on its effectiveness in early syphilis *(6)* (see Annex 5). No western studies have evaluated the use of cephalosporins in late latent disease, although as mentioned in the Augenbraun review, it appears to be commonly used in the United States *(47)*.

Neurosyphilis

Neurosyphilis can either be asymptomatic (i.e. with CSF changes but no signs or symptoms of clinical disease), or symptomatic. It is also divided into early (<1 year after infection), and late forms (which occur 4–40 years after infection) *(66)*. The diagnosis of neurosyphilis is very complex and controversial, which compounds the difficulty in achieving a consensus about the best methods for its treatment. A study by Hahn et al. of 765 patients with asymptomatic neurosyphilis showed various penicillin regimes were effective in preventing progression to neurosyphilis (3% cumulative rate of progression to symptomatic neurosyphilis at seven years) *(67)*. However comparative efficacies of different regimes could not be concluded from this study. The general basis of treatment depends on achieving an anti-treponemicidal level of antibiotic in the CSF *(68–70)*. None of the guidelines propose using BBP for neurosyphilis as it fails to achieve these levels. In the comparative study of BBP compared with PBP in asymptomatic neurosyphilis by Smith et al. (discussed in the early syphilis section) the high CSF relapse rate with BBP indicates this *(19)*.

Short acting IV benzyl penicillin is the treatment of choice in CDC guidelines, as this gives adequate treponemicidal levels in the CSF *(68–71)*. Second line treatment is PBP plus probenecid. Both of these regimes are for 10–14 days. The first line treatment in the United Kingdom is PBP plus probenecid for 17 days. In support of PBP the Hellerstrom and Skog study using procaine penicillin in 38 cases (both symptomatic and asymptomatic neurosyphilis) showed some resolution of serology, and clinical improvement in symptomatic neurosyphilis *(64)*. Dunlop et al. showed treponemicidal levels in the CSF in twelve patients *(72)*. However, the Augenbraun and Rolfs review *(18)* quotes two studies comprising a small number of case reports which suggest that CSF abnormalities and symptomatic neurosyphilis may not resolve with PBP *(73,74)*. In addition, a study reported by van der Valk et al., suggested that 40 patients with neurosyphilis given PBP, did not show treponemicidal levels of drug in the CSF *(75)*, nor did a case reported by Yoder *(76)*. In his review Goldmeier considers whether treponemicidal levels in the CSF are actually necessary for successful treatment or whether the efficacy of penicillin treatment in neurosyphilis is achieved through action in end arteries or periarteries *(9)*. If this were so, it may explain why PBP might be clinically effective even if treponemicidal levels in the CSF were not achieved.

The recent CDC report *(47)* considers adding a dose of BBP after treatment for neurosyphilis, to cover latent infection not treated with the 10–14 days proposed in the guidelines. It suggests that this would be safe and reasonable, but there is currently no evidence to support this.

United Kingdom guidelines recommend benzyl penicillin as an alternative treatment and also sanction the use of oral amoxycillin with probenecid. These regimes are for 17 days. Amoxycillin/probenecid regimes have been reported to achieve treponemicidal levels in CSF in two small studies (7 and 17 patients, but these did not report clinical outcomes *(65,77)*. European guidelines recommend benzyl penicillin as first line, with PBP as second line treatment.

The use of steroids is recommended in the United Kingdom and European guidelines for consideration in all patients with neurosyphilis, but not mentioned in the CDC guidelines. In the Russian Federation guidelines it is recommended for patients with psychotic symptoms, cerebral or spinal cord gummata. It is believed that this may limit the Jarisch-Herxheimer reaction; however; there is no evidence of prevention of the reaction in patients given steroids with treatment for *Borrelia* (which also causes this reaction).

Alternatives are limited, with European and United Kingdom citing doxycycline as the drug of choice (200 mg bd po for 28 days), despite limited data. Whiteside and colleagues studied five patients who achieved adequate CSF levels with 200 mg bd of doxycycline *(78)*. The CDC favours ceftriaxone, or penicillin desensitisation. There is minimal clinical data supporting ceftriaxone, although there is some biological evidence for its use. Two small studies have suggested that ceftriaxone is efficacious in treating HIV positive patients with neurosyphilis *(79,83)*.The trials are summarized in Table 7 *(79–83)*.

Neurosyphilis in Russian Federation is also treated with benzyl penicillin or PBP, used in the same way as the United Kingdom, CDC guidelines. However amoxycillin/probenecid treatment is avoided. Ceftriaxone is used as an alternative in penicillin allergy. There has been a Russian review written on efficacy of treatment of neurosyphilis, covering a wide range of different treatments including ceftriaxone and a small number of patients, but this review does not add any information on comparative regimes *(6)* (see Annex 5).

HIV Infection

The advent of HIV infection has led to considerable debate about the effectiveness and appropriateness of the regimes used for treating all stages of syphilis *(86–97)*. The controversy was catalysed by a number of case reports on failure of syphilis treatment in patients with HIV, and on increased severity of infections in HIV positive patients *(84,85,28–34)*. As HIV is a new infection there is difficulty in assessing this data objectively due to a significant potential reporting bias. In his article Musher reviews the evidence for both an accelerated course of syphilis infections in HIV positive patients, and for a higher rate of syphilis treatment failure *(66)*.

Other trials specifically addressing treatment in HIV infection are reviewed by Augenbraun and Rolfs *(18)*. These include a study by Goeman et al. with 193 sex workers in Zaire *(98)*. The patients were treated with CDC standard therapy (BBP three doses). Serological response rates were similar in HIV positive and negative patients, with no clinical relapse. However, this was a cohort study with large loss to follow up, HIV seroconversion during follow up in some patients, and no stage of syphilis was noted (likely late latent disease). Schofer et al. retrospectively studied 100 HIV positive patients treated for late latent or neurosyphilis as per CDC guidelines, which showed multiple relapses for neurosyphilis *(99)*. However in the study by Rolfs and colleagues discussed earlier *(21)* the absence of evidence of undesired clinical sequelae or clinical treatment failure in the HIV positive group has helped to allay fears about whether

current treatment is adequate. The difficulty in interpreting evidence in HIV positive patients is compounded by the fact that many patients may currently be receiving anti-retroviral therapy, thereby boosting their immune systems. However, it is not known what will happen to those patients in the long term if they fail on their anti-retroviral treatments and have a reduction in their CD4 counts.

This new evidence looking at HIV and syphilis co-infection has led to many of the conclusions about treatment regimes in all stages of disease, both in HIV positive and negative patients. In the main, the guidelines propose that treatment for syphilis in patients with HIV should be no different from guidelines in HIV negative patients. Specific differences in treatment are as follows; the CDC guidelines suggest a possible three dose of benzathine penicillin at day 1, day 8 and day 15 in early syphilis. Due to concern about higher levels of asymptomatic neurosyphilis in HIV positive patients (Rolfs study found a higher level of CSF changes in the HIV positive group) CDC recommends the examination of CSF in all HIV positive individuals with late syphilis and consideration of this in early syphilis. United Kingdom guidelines propose treating all HIV positive patients with treatment for neurosyphilis. CSF examination is advisable in all HIV positive patients in the European guidelines; otherwise treatment is the same as for HIV negative patients. There are no specific guidelines for the treatment of HIV/syphilis co-infected patients in Russian Federation.

It is recommended in all guidelines that all patients who are diagnosed with syphilis should be tested for HIV.

Syphilis in Pregnancy

To add to a complex situation in terms of pathogenesis and treatment of syphilis, the challenge in pregnancy is finding treatment which will treat the mother adequately, while not harming the fetus, and either treat or prevent infection in the fetus. A recent Cochrane review has looked at the various regimes used *(100)*. Singh and McCloskey have written a review article on syphilis in pregnancy that also mentions Australian guidelines *(101)*. As in other areas of syphilis management there has been no comparison made about the relative efficacy of different penicillins *(5)*.

The CDC guidelines recommend using the same regimes as for the relevant stage of syphilis as in non-pregnant patients but with a possible second dose at day 8 for BBP in early syphilis *(5)*. This is based on research showing that due to physiological changes in pregnancy a single IM dose of 2.4 mu benzathine penicillin remains at treponemicidal levels (>0.018 μg/ml) in serum for three times longer in non-pregnant than pregnant women *(102)*. Watson-Jones et al. completed a prospective cohort trial of 1688 pregnant women in Tanzania *(103)*. A total of 382 women with positive syphilis serology were given a single dose of BBP (2.4mu IM). This showed no increased risk of adverse pregnancy outcome for women with positive syphilis serology treated with BBP compared with 950 seronegative women. Stillbirth rate was 2.3% in seropositive treated women and 2.5% in seronegative women. Low-birth-weight live births were 6.3% in seropositive treated women and 9.2% in seronegative women. Alexander and colleagues followed CDC guidelines (i.e. single dose BBP) in 448 pregnant women with early syphilis, with a success rate of 98.2% in preventing congenital syphilis *(104)*. However, a study in Africa found if two doses of BBP one week apart were used in pregnant women with early syphilis there were lower rates of congenital syphilis and infant mortality, with higher birth weights *(25)*. A PBP regime is recommended in the United Kingdom guidelines reflecting concern over

reports of treatment failure of benzathine penicillin in pregnant women *(24–27,105)*. European guidelines recommend BBP (2 doses) and PBP as second line. There is no evidence for teratogenicity with penicillin *(106)*.

Options for pregnant women who are allergic to penicillin are limited. Use of tetracyclines is contraindicated in pregnancy due to the possible effects on the fetus (animal studies show skeletal developmental abnormalities and there is possible dental discolouration). Erythromycin does not cross the placenta well, as discussed earlier, but is still included in the United Kingdom guidelines *(107)* but with treatment of babies at birth with penicillin. Azithromycin has not been tested in pregnancy, but in non-pregnant patients the results look promising. The biological plausibility for the efficacy of ceftriaxone is also good, but again this has yet to be tested clinically. Although United Kingdom guidelines recommend azithromycin and erythromycin, the treatment of choice in this situation for CDC and European guidelines is penicillin desensitisation, with European guidelines including ceftriaxone. There is a consensus that retreatment of the mother with doxycline should be given after breastfeeding if these oral treatments have been used, and it is suggested that infants of these patients also receive treatment for congenital syphilis to cover the possible failure of these antibiotics.

The Russian Federation guidelines are more specific depending on the stage of gestation and stage of syphilis. Up until 18 weeks the treatment is as for non-pregnant adults, including use of BBP. PBP is recommended as the first choice in later gestational periods (>18 weeks), with NBP as an alternative. New guidelines not yet issued may recommend avoiding BBP in all stages of pregnancy *(41)*. Research in Russian Federation showed a good response with NBP in early syphilis on 53 patients with good serological responses and no cases of congenital syphilis *(6)* (see Annex 5). Benzyl penicillin is also recommended.

Congenital Syphilis

There is little evidence for the comparative efficacy of different regimes in congenital syphilis. Treatment strategies are therefore based on extrapolation of experience with penicillin in treating other forms of syphilis, with dose adjustment for infant weight. CDC, United Kingdom and European guidelines use benzyl penicillin as the first line, since treatment is delivered on an inpatient basis, and there are difficulties in assessing differences in the pharmacological behaviour of drugs in infants. Chang and colleagues used benzyl penicillin, which showed at 12 months the serological response for VDRL was 100% and for TPHA was 95% *(108)*. CDC and United Kingdom guidelines include PBP, and European guidelines also include BBP. There is some concern over sodium load in procaine penicillin. In practice it may be difficult to give neonates a dose of BBP as the solution is very viscous and needle size small (personal correspondence with M Temmerman). Penicillin allergy was not considered, or desensitization to penicillin recommended.

The Russian Federation guidelines are divided into early and late, and use soluble penicillin as first line but also include long acting penicillins. 100 000 IU/kg/day of Benzyl penicillin is split into more frequent doses (i.e. every four hours), but this practice may change *(41)*. The guidelines employ a longer duration of treatment for both early and late syphilis, and incorporate a break in treatment in late congenital syphilis. Ceftriaxone is recommended in Russian Federation for penicillin allergy in congenital syphilis.

Epidemiological Treatment of Contacts

There is widespread agreement that all patients with syphilis should have contact tracing performed. The question of whether to treat an asymptomatic contact or to wait for signs is more difficult. The stage of disease of the patient with syphilis is important as some stages are much more infectious, i.e. secondary than others. CDC guidelines recommend presumptive treatment (i.e. one dose BBP) for contacts within the last 90 days. The United Kingdom guidelines recommend BBP single 2.4 MU dose or doxycycline 100 mg bd for 14 days. Azithromycin 1 g stat is second line. The European guidelines do not recommend routine treatment. A recent study in the United States revealed that azithromycin might be efficacious in treating incubating syphilis *(51)*. In Russian Federation all patients with sexual or close domestic contact with a syphilis-infected person in the last two months are treated. Regimes are one dose of BBP, two doses of bicillin-3 (1.8 million units/dose), or bicillin-5 (1.5 million units/ dose). Alternatives are PBP (1 million units/day for seven days) or NBP (600 000 units/twice a day for seven days). Potential infections through blood transfusion in the last three months are also treated in this manner.

Conclusions

The purpose of this paper was to compare the differences in international treatment regimes for syphilis in Europe. WHO estimates that around 11 million new cases of syphilis are occurring worldwide every year *(8)*, with the bulk of these occurring in South-East Asia (4m) and Sub-Saharan Africa (3.8m), in the WHO European Region much higher syphilis rates are observed in eastern Europe and central Asia than in western or central Europe *(115–118)*. While parenteral penicillin based regimes are highly effective, parenteral regimes are not ideal for use in many settings. There is still a lack of evidence to identify and build consensus on the most appropriate regimes for different stages of disease. With the advent of HIV infection, and the mobility of population groups leading to increasing levels of syphilis in many geographical regions, the need for effective treatment and harmonized treatment guidelines is greater than before.

This review points to the need for formal comparative clinical trials of syphilis treatment. While many of the guidelines are based on the same clinical evidence, the differing conclusions drawn by experts from different geographical regions highlight this need. The report has highlighted some of the areas of disagreement, which may be important to study in the future. These include comparisons of different penicillins, penicillin alternatives, parenteral vs. oral treatments, and comparison of dose and duration for maximum efficacy with minimal drug use.

It is unlikely that the pharmaceutical industry can be expected to deliver these studies. Control of syphilis should be considered a public good and public resources need to be found to take forward the necessary research. Logistical problems in conducting clinical trials, which arise from inadequate numbers of cases occurring in those countries where the bulk of the worldwide clinical research effort is carried out could be overcome by supporting the development of trials in countries which have high incidence, but also the technical infrastructure to conduct these – such as some countries of the newly independent states. Further basic research, particularly in relation to developing better and more rapidly measurable outcome measures for treatment, would considerably facilitate the conduct of such trials.

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Tables

Table 1

Summary of Different Penicillin Preparations						
Abbreviation used in this paper	**Names given in different papers**	**Components**	**Equivalent dose for 1 million units benzyl penicillin**	**Peak concentration (time after IM injection)**	**Duration of action**	**CSF penetration**
Benzyl Penicillin	Benzyl Penicillin SBP	Penicillin G Potasium or Penicillin G Sodium	600 mg	15–30 min	t1/2 = 30min	good
BBP	Benzathine Penicillin Extencillin Retarpen Bicillin-1	Benzathine Penicillin G	750 mg	240 min	Detectable in plasma for 4 weeks	poor
PBP	Procaine Penicillin	Procaine Penicillin G	1020 mg	60–240 min	Effective concentrations in plasma for 12–24 hours	poor
NBP	Novocaine salt	Procaine Penicillin with novocaine salt	1020 mg		Shorter acting than PBP, so given bd instead of od	poor
Bicillin -3	Bicillin -3	BBP, Benzyl Pen, NBP in 1:1:1 ratio	n/a	n/a	Intermediate	
Bicillin -5	Bicillin -5	BBP, NBP in 1:4 ratio	n/a	n/a	Intermediate	

Table 2a

Early Syphilis (Primary/Secondary/Early Latent <2 years)									
		Alternatives				**Penicillin allergy**		**Parenteral treatment refused**	
Europe	Treatment	BBP	PBP	Benzyl Penicillin		Doxycycline	Ceftriaxone	As penicillin allergy	
	Dose	2.4 MU	600 000 units	1 MU		200 mg	250–500 mg		
	Regime	ow	od	qds		od	od		
	Route	IM	IM	IM		po	IM		
	Duration	1 week	10–14 days	10–14 days		14 days	10 days		
United Kingdom	Treatment	PBP	BBP			Doxycycline	Azithromycin	Amoxycillin/ Probenecid	As penicillin allergy
	Dose	750mg	2.4 MU			100 mg	500 mg	2g/500mg	
	Regime	od	ow			bd	od	qds	
	Route	IM	IM			po	po	po	
	Duration	10 days	1 or 2 weeks			14 days	10 days	14 days	
United States	Treatment	BBP				Doxycycline	Ceftriaxone	As penicillin allergy	
	Dose	2.4 MU				100mg	1g		
	Regime	ow				bd	od		
	Route	IM				po	IM		
	Duration	1 week				14 days	10 days		

od: once daily; bd: twice daily; tds:3 x daily; qds: 4 x daily

ow: once weekly; bw: twice weekly

Table 2b

Early Syphilis (Primary/Secondary/Early Latent <2 years)								
		Alternatives				**Penicillin allergy**		**Parenteral treatment refused**
Russian Federation	**Primary**							Not applicable
	Treatment	BBP/Bicillin-1	Bicillin-3/Bicillin-5	PBP/NBP	Benzyl Penicillin	Doxycycline	Azithromycin	
	Dose	2.4 MU	1.8 MU/1.5 MU	1.2 MU/ 600 000 units	1 MU	100 mg	500 mg	
	Regime	ow	bw	od/bd	qds	bd	od	
	Route	IM	IM	IM	IM	po	IM	
	Duration	2 weeks	total of 5 doses	10 days	10 days	15 days	10 days	
	Secondary/Early Latent							
	Treatment	BBP/Bicillin-1	Bicillin-3/Bicillin-5	PBP/NBP	Benzyl Penicillin	Doxycycline	Azithromycin	Not applicable
	Dose	2.4 MU	1.8 MU/1.5 MU	1.2 MU/ 600 000 units	1 MU	100 mg (?)	500 mg	
	Regime	ow	Bw	od/bd	qds	bd	od	
	Route	IM	IM	IM	IM	po	po	
	Duration	3 weeks	total of 10 doses	20 days	20 days	30 days	10 days	

Table 3

Late latent/cardiovascular/gummatous						
		Alternatives			**Penicillin allergy/parenteral treatment refused**	
European	Treatment	BBP	PBP	Benzyl Penicillin	Doxycycline	Tetracycline
	Dose	2.4 MU	0.6 MU	1 MU	200 mg	500 mg
	Regime	ow	od	od	od	qds
	Route	IM	IM	IM	po	po
	Duration	3 weeks	17–21 days	21 days	21–28 days	28 days
United Kingdom	Treatment	PBP	BBP		Doxycycline	Amoxycillin/ probenecid
	Dose	750 mg	2.4g		200 mg	2 g/500 mg
	Regime	od	ow		bd	tds/qds
	Route	IM	IM		po	po
	Duration	17 days	3 weeks		28 days	28 days
United States	Treatment	BBP			Doxycycline	Tetracycline
	Dose	2.4 MU			100 mg	500 mg
	Regime	ow			bd	qds
	Route	IM			po	po
	Duration	3 weeks			28 days	28 days
Russian Federation	Treatment	Benzyl Penicillin	NBP	PBP	Ceftriaxone	
	Dose	1 MU	0.6 MU	1.2 MU	1–2 g	
	Regime	qds	bd	od	od	
	Route	IM	IM	IM	IM	
	Duration	28 days , 14 days off, 14 days	28 days , 14 days off, 14 days	20 days, 14days off, 10 days, (28 days in late visceral)	14 days	

Table 4

Neurosyphilis						
European		**Alternatives**			**Penicillin Allergy**	
	Treatment	Benzyl Penicillin	Benzyl Penicillin	PBP + Probenecid	Doxycycline	
	Dose	2-4 MU	0.15 MU/kg/day	1.2–2.4 MU/500 mg	200 mg	
	Regime	over 6 doses/day	over 6 doses/day	od/qds	bd	
	Route	IV	IV	IM/po	po	
	Duration	10–21 days	10–14 days	10–21 days	28–30 days	
United Kingdom	Treatment	PBP + Probenecid		Benzyl Penicillin	Doxycycline	
	Dose	2g/500 mg		18–24 MU	200 mg	
	Regime	od/qds		Over 6 doses/day	bd	
	Route	IM/po		IV	po	
	Duration	17 days		17 days	28 days	
United States	Treatment	Benzyl Penicillin	PBP + Probenecid		Ceftriaxone	Or penicillin desensitization
	Dose	18–24 MU	2.4 MU/500 mg		2 g	
	Regime	Over 6 doses/day or cont infusion	od/qds		od	
	Route	IV	IM/po		IM/IV	
	Duration	10–14 days	10–14 days		10–14 days	
Russian Federation		**Early visceral neurosyphilis**			**Early Neurosyphilis**	
	Treatment	Benzyl Penicillin	NBP		Benzyl Penicillin	Benzyl Penicillin
	Dose	1 MU	0.6 MU		10 MU	2 MU
	Regime	qds	bd		bd	6/day
	Route	IM	IM		IV	IV
	Duration	20 days	20 days		14 days	14 days
		Late Visceral Neurosyphilis				
					Penicillin Allergy	
	Treatment	Benzyl Penicillin	NBP	PBP	Ceftriaxone	
	Dose	0.4 MU	0.6 MU	1.2 MU	1–2 g (up to 4 g)	
	Regime	8/day	bd	od	od	
	Route	IM	IM	IM	IM/IV	
	Duration	28 days, 14 days off, 28 days	28 days, 14 days off, 28 days	42 days, 14 days off, 14 days	14 days	

Table 5

Pregnancy						
		Alternatives		**Penicillin Allergy**		
European	Treatment	BBP	PBP	Desensitisation to penicillin	Azithromycin	Ceftriaxone
	Dose	2.4 MU	0.6/1.2 MU		500 mg	250–500 mg
	Regime	ow	od		od	Od
	Route	IM	IM		po	IM
	Duration	2 weeks	10–14 days		10 days	10 days
					Consider retreatment with doxycycline after breastfeeding if given above treatments	
United Kingdom	Treatment	PBP		Erythromycin	Azithromycin	Desensitization to penicillin
	Dose	750mg		500 mg	500 mg	
	Regime	od		qds	od	
	Route	IM		po	po	
	Duration	10 days		14 days	10 days	
				Consider retreatment with doxycycline after breastfeeding if given above treatments		
United States		As per protocol for relevant stage of disease, but possible additional dose of Benzathine Penicillin at day 8		Desensitization to penicillin		
Russian Federation		Up to 18 weeks gestation	Post 18 weeks gestation			
			Primary			Secondary/ early latent
	Treatment	As per protocols for relevant stage of disease	PBP	NBP	Benzyl Penicillin	PBP
	Dose		1.2 MU	600 000units	1 million units	1.2 MU
	Regime		od	bd	qds	od
	Route		IM	IM	IM	IM
	Duration		10 days	10 days	10 days	20 days
		Penicillin Allergy				
	As per previously described protocols but avoiding tetracycline; children are treated with penicillin at birth					

Table 6

Congenital						
						Penicillin allergy
European	Treatment	Benzyl Penicillin	PBP	BBP if CSF normal		No guidelines
	Dose	150 000 units/kg	50 000 units/kg	50 000 units/kg		
	Regime	Over 6 doses/day	od	od		
	Route	IV	IM	IM		
	Duration	10–14 days	10–14 days	1 day		
United Kingdom	Treatment	Benzyl penicillin		PBP		No guidelines
	Dose	50 000 units/kg		50 000 units/kg		
	Regime	bd	then tds	od		
	Route	IV	IV	IM		
	Duration	7 days	3 days	10 days		
United States	Treatment	Benzyl Penicillin		PBP	BBP*	Penicillin Desensitization
	Dose	50 000 units/kg		50 000 units/kg	50 000 units/kg	
	Regime	bd	then tds	od	ow	
	Route	IV	IV	IM	IM	
	Duration	7 days	3 days	10 days	1 day	
Russian Federation		**Early Congenital Syphilis**				
						Penicillin allergy
	Treatment	Benzyl peniclin	NBP	PBP	BBP	Ceftriaxone or Oxacillin or Ampicillin
	Dose	100 000 u/kg	50 000 u/kg	50 000 u/kg	50 000 u/kg	100 000 u/kg
	Regime	Over 6 doses/day	Over 2 doses/day	od	Ow	Over 4 doses/day
	Route	IV	IM	IM	IM	IM
	Duration	14 days	14 days	14 days	3 weeks	14 days
					Only if CSF normal & not >2 kg	
	Late congenital syphilis					
						Penicillin allergy
	Treatment	Benzyl Penicillin	NBP	PBP		No guidelines
	Dose	50 000 u/kg	50 000 u/kg	50 000 u/kg		
	Regime	Over 6 doses/day	Over 2 doses/day	od		
	Route	IV	IM	IM		
	Duration	28 days, 14 days off, 14 days	28 days, 14 days off, 14 days	28 days, 14 days off, 14 days		

* Normal examination + titres, mother untreated; non penicillin regime see text of guidelines for more details

Table 7

Evidence for Non Penicillin Treatments								
Authors	**Ref**	**Design of study**	**Patients**	**Dose**	**Assessment of Outcome**	**Serological outcome**	**Clinical relapse**	**Follow up**
Harshan V, Javakumar W 1982	109	Open, non-randomized, non-comparative study of **doxycycline** in early syphilis	**n=40** P/S/E	100 mg od for 15 days	VDRL titre reduced by <2 dilutions	After 6 weeks to 9 months 6 became seronegative. 9 had low titres	0	20 patients completed treatment. 7 patients had low titres at 3 years. Others lost to follow up
Yoichi Onada 1979	110	Open, non randomized, non comparative study of oral **doxycycline**	**n = 51** P E- 5 S – 10 AC – 20 LL – 16	100 mg bd for 28 days, repeated every 3 or 4 months for 2–93 months	WR/VDRL tests (excellent/good response if one or both titre decrease by 2 or more dilutions)	Good/excellent response; P – 100%, EL – 90%, AC – 90%, LL – 68%	Not published	2–93 months
Schoeter AL , Lucas JB, Price EV, Falcone VH 1972	111	Multicentre, prospective, non-randomized, treatment comparison of **PPB, BBP, tetracycline, erythromycin**	**n = 586** P/S PBP – 162 BBP – 100 Erythromycin (30g) – 144, (20g) – 71 Tetracycline – 107	PBP 4.8 MU IM BBP 2.4 MU IM, Doxycycline 2 g/day for 10 days or 3 g/day for 10 days Tetracycline 3 g/day for 10 days	Included VDRL, FTA-abs, TPI. No definitive response documented. Patients assessed for clinical signs/decrease in titres	Not definitively documented, but retreatment rates assessed; at 6 months (53 patients) PPB = 3.6% BBP = 3.4% Erythromycin 30g = 4.1% 20 g = 18.3% Tetracycline = 5.3%		37 patients at 24 months. Retreatment rates PPB = 10.8% BBP = 11.4% Erythromycin 30g= 21.3% 20g= 29.9% Tetracycline = 12.7%
Fernando WL 1969	112	Non-randomized, prospective, single centre trial study of **erythromycin**	n=34 P – 20 S – 13 E – 1	500 mg 6 hourly for 10 days (20g total)	Clinical resolution and VDRL seronegativity. CSF examination in 7 cases at 16 - 24 months	Seronegative rates at end of follow up P – 16 S – 7 E – 0	No clinical relapse. All CSF tests normal	22 patients to 6 months 4 patients to 24 months
Hook III EW, Roddy RE, Handsfield HH. 1988	81	Prospective, non-randomized, non-comparative trial of **ceftriaxone**	**n = 21** P/S	250 mg/day for 10 days or 500 mg every 48 hours for 5 doses	VDRL seronegativity or 4-fold decrease in VDRL titres	9 patients become seronegative	No treatment failures	Serology performed on 16 patients at 12 weeks
Moorthy TT, Lee CT, Lim KB, Tan T. 1987	82	Randomized, open comparison study of **ceftriaxone** and **BBP**	**n = 21** all P	(i)Ceftriaxone 3 g one dose (ii)Ceftriaxone 2g/day 2 doses (iii)Ceftriaxone 2g/day 5 doses (iv)BBP 2.4 mu IM once	Seronegativity	Seronegative by 6 months i – 2/ ii – 3/5 iii – 0/3 iv – 2/5	1 patient was retreated in the regime, none in other regimes	18/21 followed to 6 months 17/21 followed to 12 months
Katsambas A, Adoniou C, Katsarou A, Kerkidou A, Stratigos J. 1987	113	Randomized comparison study of **Ceftriaxone** and **BBP**	**n = 36** P/S 18 in both treatment groups	Ceftriaxone 1g/ day every 3 days for 4 doses BBP 11.2 mu total over 35 days	VDRL failure if > 4-fold dilution from baseline or by clinical lesions	0 failures	0 failures	94% both groups for 3 months 73% both groups for 6 months

Authors	Ref	Design of study	Patients	Dose	Assessment of Outcome	Serological outcome	Clinical relapse	Follow up
Schofer H, Vogt HJ, Milbradt R 1989	114	Prospective, randomized, open, multicentre, comparative study of **ceftriaxone** and **BBP**	**n = 28** P/S 14 in both treatment groups	Ceftriaxone 1 g every 48 hours for 4 doses PPB 1 million units od for 15 days	Clinical resolution and VDRL titre decrease by > 2 dilutions	0 failures	0 failures	8 patients to 6 months and 12 patients to 12 months
Dowell MR, Ross PG, Musher DM, Cate TR, Baughn RE. 1992	83	Randomized, prospective, trial of **ceftriaxone** and **BBP** in HIV positive patients with late/neurosyphilis	**n = 56** NS/LL ceftriaxone - 43 BBP – 13	1–2g Ceftriaxone /day for 10–14 days; BBP 2.4 mu, 3 doses at weekly intervals	Serological response - VDRL, RPR, MHA-TP >four-fold decrease, or clinical progression to neurosyphilis	Ceftriaxone; 65% response, 12% serofast, 21% serological relapse; BBP 62% response, 8% serofast, 15% serological relapse	1 patient with ceftriaxone and 2 with BBP progressed to symptomatic neurosyphilis	All 43 receiving ceftriaxone and all 13 receiving BBP followed to 16 months
Verdon MS, Hansfield HH, Johnson RB. 1994	50	Open, non comparative pilot study of **azithromycin**	**n = 16** P – 10 S – 6 (all HIV negative)	500mg daily for 10 days	Clinical resolution and RPR decrease > 2 dilutions after 3 months or to negative by 6 months	8 patients negative serology by 6 months	1 failure/ reinfection 1 indeterminate	14 patients followed to 6 months
MashkilleysonAl, Gomberg MA, Mashkilleyson N, Kutin SA. 1996	52	Open, comparative, non-randomized trial of **Azithromycin**, **Erythromycin, Benzyl penicillin** and **BBP**	**n = 523** all E Azithromycin -100 Erythromycin – 60 Benzyl Penicillin – 160 BBP – 203	Azithromycin 500mg od 10 days/ 500mg alt days for 11 days Erythromycin 2g od for 15 days Benzyl Penicillin 300 000IU IM 3 hourly for 16-30days BBP 2.4MU IM once/2 doses day 1 and 8	Clinical resolution and Wasserman reaction. In some patients TPI and FTA-abs noted	Of 93 seropositive patients treated with azithromycin - 88 resolved by 6 months and 91 by 15 months. All those treated with daily azithromycin had serological resolution by 4 months	Multiple clinical responses studied, with azithromycin comparing well or healing signs quicker than other treatments	3–4 year follow up? All patients followed up for this time period
Gruber F, Kastelan M, Cabrijan L, Simonic E, Brajac I. 2000	53	Open non comparative trial of **azithromycin**		1g initially then 500mg daily for 8 days	Clinical resolution and VDRL titre reduction by at least four-fold	All patients had at least a four fold reduction at 6 months	All patients had clinical response	14 at 6 months
Hook EW III, Stephens J, Ennis DM. 1999	51	Single centre, open labelled randomized pilot study of **azithromycin** and **penicillin** for incubating syphilis	n = 96 azithromycin – 52 penicillin – 44	One dose of 1g azithromycin One dose of BBP 2.4MU IM	No evidence of syphilis clinically or serologically at outset. Clinical examination. RPR and FTA-abs serology	No patients in either group developed seropositivity	No patients in either group devolped clinical syndrome	Followed for 3 months. 63 evaluable patients (63%). More non evaluable in the penicillin group (12 vs 21)

Abbreviations
P – primary
S – secondary
E – early
NS – neurosyphilis
LL – Late Latent
AC – Adult congenital
EL – Early Latent

Annex 1

GOH BT, VAN VOORST VADER PC: EUROPEAN GUIDELINES FOR THE MANAGEMENT OF SYPHILIS. INTERNATIONAL JOURNAL OF STD & AIDS, 2001; 12 (SUPPL 3): 14–26

Available in pdf at: http://www.iusti.org/

Annex 2

UK NATIONAL GUIDELINES ON THE MANAGEMENT OF EARLY SYPHILIS

Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases.
Draft Document 2002.

Available in pdf at: http://www.mssvd.org.uk

Annex 3

UK NATIONAL GUIDELINES ON THE MANAGEMENT OF LATE SYPHILIS

Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases.
Draft Document 2002.

Available in pdf at: http://www.mssvd.org.uk

Annex 4

CENTERS FOR DISEASE CONTROL AND PREVENTION. SEXUALLY TRANSMITTED DISEASES TREATMENT GUIDELINES 2002. MORBIDITY AND MORTALITY

Weekly Report, 2002; 51: No RR-6.

Available in pdf at: http://www.cdc.gov/std/treatment/

Annex 5

AKOVBIAN V, FILATOVA E. MANAGEMENT OF SYPHILIS INFECTED PATIENTS IN RUSSIA. COUNTRY BACKGROUND PAPER, MAY 2002. (ORIGINAL IN RUSSIAN; TRANSLATED IN ENGLISH)

Management of Syphilis Infected Patients in Russia (English translation)

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Background

The system of the STI control in the former USSR including the responsibility of a patient in base of the article 115 of the USSR Criminal Code, medical staff's duties, treatment schemes, and the order of further observation of a patient within the following five years was strictly regulated (Instructions given by USSR Health Ministry methodical recommendations).

Methodical Guidelines were distributed through DVS clinics only and were inaccessible for other specialists. Before the 1976 syphilis treatment was conducted only in inpatient clinics. A syphilis positive patient was to be hospitalized within 24 hours after having received the positive test.

Since 1976 outpatient treatment prescription has become allowed for people who had registration at the place of living (propiska) and job. By the government's opinion this allowed people to continue their treatment up to the end. If a person declined from syphilis treatment he was to be punished by law. According to article 115 of the Soviet Criminal Code these persons were subjected to one year imprisonment, where they got suitable treatment. In the 1980s about 1000 people per year were condemned for this reason *(1)*.

Nowadays some of syphilis infected people (pregnant women, children, elderly people and people with other diseases) get treatment in DVS stationary clinics. People related with behavioural risk: homeless, sex workers, criminals, etc. go through compulsory treatment in closed guarded inpatient clinics. Usually 20% of all of notified syphilis people get stationary treatment.

The evolution of national "Syphilis treatment and prevention instructions" from 1932 to 2002

The document describing ways of syphilis treatment, obligatory for application in the former USSR and Russian Federation, was called "Methodical Guidelines" or "Methodical instructions". It was issued every 5–7 years. During the last 70 years about 20 similar documents totally have been published. The main ones are presented in Table 1.

The Central DVS Institute develops new methods of syphilis and other STI treatment, releasing the instructions confirmed by the Health Department. In the time of the USSR new antibiotics were sent to some leading scientific centres and clinics (Dermatovenereology Institutes, high

school pulpits), where clinical tests of new preparations were conducted along the same scheme. The results were worked up and searched in the Central DVS Institute, later the final results were discussed at the conferences and were conveyed to the Health Ministry for assertion. Any research studies made abroad were never considered or discussed.

After the USSR disintegration these schemes have stopped working. Today the scientists chosen and surveyed by the Central DVS Institute syphililology department give their advice and recommendations, which play most significant role.

Different publications on this subject inside of the country are discussed, generalized and presented in theses and reviews.

Clinical efficasy of all investigated drugs were done by following free design without randomization procedure and quite often without a setting up a control group. Therefore the received data analysis is difficult due to non-uniformity of patients and the absence of data estimation criteria. Nowadays foreign researchers' opinions are highly evaluated and considered. Besides, the instructions on syphilis treatment and prevention, developed abroad (CDC, for example) are of main interest.

The first episodes on penicillin usage for venereal diseases treatment happened in the 1943. It started in the Soviet Army, where they received American penicillin by the land-lease system. The first articles on the results of syphilis diseased patients' treatment were issued by the Military Medical Academy in 1945.

The usage of soluble penicillin appeared in the "Medical instructions" in 1948. Previously arsenic, bismuth, mercury, and iodine salts were the main preparations for syphilis treatment. Because of the toxicity of the heavy metals this treatment was divided into several courses, off and on. The interval between the application of the courses was around one month. The number of the treatment courses depended on diagnosis and varied from three courses (primary syphilis) to eight courses (late syphilis). The whole treatment including intervals might last more than one year.

From the 1962 home manufactured long-lasting preparations of Penicillin, Ecmonovocillin (the mixture of Penicillin Novocaine salt and Ecmolin), Bicillin-1 (Benzatinbenzyl penicillin), Bicillin-3 (the mixture of Benzylpenicillin, Novocaine salt of Penicillin and Benzatinbenzyl penicillin in equal parts) were introduced into the "Medical recommendations".

The interesting thing is that although being easy for usage and being effective, the long-lasting preparations didn't take a leading place in the syphilis therapy, they had been still prescribed side by side with soluble penicillin, bismuth, and arsenic for more than 20 years.

In 1976 the resolution to treat syphilis in one course was adopted. The penicillin dosage was summarized and equalled the quantity of the preparation used in a number of courses. This decision was very significant as it gave an opportunity for outpatient treatment with the usage of long-lasting penicillin preparations. And although this treatment was allowed for only limited group of patients, still the experience gave doctors an opportunity to see the advantages of the method.

The period 1981–1988 was revolutionary because arsenic and bismuth preparations were cancelled. So the era of syphilis treatment by extremely harmful preparations had ended. Some other preparations were introduced, such as erythromycin, tetracycline, etc. This allowed for syphilis treatment policy more flexible.

In 1995 modern foreign manufactured lasting preparations, such as benzatinbenzylpenicillins, were introduced in the treatment schemes. Today 80% of the patients receive outpatient treatment. The outpatient treatment has given an opportunity to manage a large quantity of diseased patients while the STI epidemic.

Table 1. Basic changes in syphilis treatment policy in the former Soviet Union (and Russia) in 1932–2002

Years	The basic changes of the contents of Methodical instructions
1932	Medical preparations of heavy metals (bismuth, mercury), arsenic, iodine
1945	–
1948	Introduction in circuits of treatment of soluble penicillin
1951	–
1954	–
1962	Introduction in circuits of treatment by domestic lasting preparations of penicillin: ecmonovocillin, bicillin-1, bicillin-3.Cancellation of mercury preparations
1976	Introduction of permanent methods of treatment with lasting preparations of penicillin for the separate categories, the limited introduction of outpatient treatment
1981	Arsenic preparations cancellation
1988	Bismuth preparations cancellation; course treatment cancellation. Introduction of out-patient treatment of syphilis. Introduction of alternative preparations (erythromycin, doxicycline)
1993	–
1995	The circular introduction in the circuits of treatment with foreign and domestic benzatin penicillins. The beginning of transition into total outpatient treatment
1999	Increase in single dozes of soluble penicillin up to one million units, reduction of duration of treatment of patients with primary and secondary syphilis by soluble penicillin. Introduction of procaine penicillin as one of the basic antibiotics and ceftriaxone, as an alternative preparations

By the present time in order to develop new guidelines on syphilis treatment the data of the modern foreign literature and separate scientists' opinions without generalized analytical processing have been used. As a rule when using foreign manufactured methods the preparation doses were increased.

For example: two injections of benzatinpenicillin, 2.4 million units for primary syphilis treatment, and three injections for secondary syphilis treatment (instead of one injection according to the CDC recommendation); or introduction of procaine penicillin in a dose 1 200 000 units per a day within 20 days (instead of 10 days on CDC), etc.

Basic contests of the Methodological Guidelines on syphilis treatment and prevention, Moscow, 1999 ***(2)***
According to this document there are the following schemes of syphilis treatment:

1. Preventive treatment
Preventive treatment is prescribed to a patient who had recently (not more than two months) had a sexual or a close domestic contact with syphilis infected person, having the early stage of the disease.

Treatment is conducted on an outpatient basis with one injection of extencillin, retarpene or bicylline-1, 2.4 million units dose, or with two injections of bicylline-3, in 1.8 million units dose or bicylline-5 in 1.5 million units dose twice a week.

Preventive treatment can be also done by procaine penicillin in a dose 1 million units once a day within 7 days, or by novocaine penicillin salt in a dose 600 000 units twice a day within 7 days as well.

Those who contacted syphilis diseased person more than 2–4 months before must go through clinical serology testing two times, once in two months. If four months passed since the contact then a serology test should be done only once.

If a person received the blood of a syphilis diseased patient while blood transfusion he is to be treated according to one of the preventive methods in case that not more than three months passed since the transfusion. If 3–6 months have passed then a patient should go through clinical serology tests two times with two months interval. More than six months after the transfusion one clinical serology test should be done.

2. Treatment of patients with primary syphilis

Method 1
Two injections of extencillin or retarpene in 2.4 million units dose should be taken with 7 days intervals, or 3 injections of bicylline-1 in 2.4 million units dose should be taken each injection once in 5 days.

Method 2
Bicylline-3 in 1.8 million units dose should be taken twice a week, totally 5 injections; or with Bicylline-5 in 1 500 000 units twice a week, 5 injections total.

Method 3
Procaine penicillin is prescribed, one dose is 1.2 million units daily during 20 days or novocaine penicillin salt 600 0000 units 2 times a day, within 10 days

Method 4
Treatment is done with intramuscular injections of water soluble penicillin in 1 million units dose every 6 hours (4 times a day) within 10 days.

3. Treatment of patient with secondary and early latent syphilis

Method 1
Treatment is done with extencillin or retarpene, 2.4 million units per injection, once a week; or with bicylline-1, 2–4 millions units per injection, once in 5 days, totally 6 injections.

Method 2
Treatment is done with bicylline-3 in 1.8 million units dose 2 times a week, totally 10 injections. Or with bicylline-5 in 1.5 million units dose, injected twice a week, totally 10 injections.

Method 3
Treatment is done with procaine penicillin – 1.2 million units per injection daily, within 20 days, or with novocaine salt 600 000 units twice a day, within 20 days.

Method 4
Water soluble penicillin in 1 million units dose is injected every 6 hours (4 times a day) within 20 days.

Note: Mostly the third and the fourth methods are prescribed for patients with "late" relapse, with alopecia and white spots, as well as for patients with early latent syphilis with over six months duration of the disease.

4. Treatment of patients with early visceral neurosyphilis

Patients with early visceral neurosyphilis should get treatment in an inpatient clinic being supervised by a clinician.

Method 1
Specific treatment is done with soluble penicillin, 1 million units per injection, taken 4 times a day within 20 days.

Method 2
Novocaine penicillin salt 600 000 units twice a day during 20 days. In all the cases symptomatic therapy is prescribed.

5. Treatment of patients with early neurosyphilis.
The decision about hospitalization of a patient with early neurosyphilis is usually undertaken by neuropathologist and dermatovenereologist on a base of severity of disease and localization of pathology.

Method 1
Intravenous dropper with benzylpenicillin sodium salt in 10 million dose twice a day within 14 days is prescribed. One dose of the antibiotic is dissolved in 400 ml of NaCl isotonic solution and applied intravenously within 1.5–2 hours. The solutions are to be used immediately after being prepared.

Method 2
Soluble penicillin (sodium) in 2 million units dose 6 times a day within 14 days is injected intravenously. One penicillin dose is dissolved in 10 ml of saline and is injected slowly, for 3–5 minutes, into elbow vein.

The decision about preventive and symptomatic treatment is discussed by consulting with dermatoveneorologist, neuropathologist, and if necessary with oculist. In six months after the treatment a control CSF test should be done. If the sanitation is absent, then treatment course should be repeated.

6. Principles of treatment of syphilis infected patients with associated STI diseases.
Syphilis infected patients must go through HIV and STI tests.

If a syphilis diseased patient has Gonorrhoea, Chlamydia infection or other genitourinary infections, then treatment is done together with syphilis treatment.

If a patient occurred HIV-positive, then he is to be sent to a regional AIDS prevention and treatment centre for further diagnostic, treatment and permanent examination at the same time following the syphilis treatment recommendations as well.

7. Treatment of patients with tertiary and late latent syphilis
Treatment of patient with tertiary syphilis and associated specific damage of inner organs is done in the same way as visceral treatment. In cases of late latent syphilis as well as having no visceral damage a patient goes through treatment according to the following methods:

Method 1
Water soluble penicillin in 1 million units dose 4 times a day, within 28 days. Then, after two weeks interval, the second treatment course is done either in the same way or with a moderate durability penicillin preparation. The second course lasts 14 days.

Method 2
Treatment is done with novocaine penicillin salt in 600 000 units dose two times a day, within 28 days.

After two weeks interval the second course in the same doses is prescribed. It lasts two weeks. Besides, procaine penicillin can be used, applied once a day, within 20 days. The second course in the same doses is applied after two weeks interval. It lasts 10 days.

8. Treatment of patients with late visceral neurosyphilis

A. Treatment of patients with late visceral neurosyphlis
The treatment is conducted by a dermatoveneorologist together with an internist, who prescribes accompanying and symptomatic therapy.

Method 1
Treatment starts with two weeks of preliminary treatment with general antibiotics (tetracycline, erythromycin) by 0.5 grams 4 times a day. Then penicillin therapy starts. Penicillin is taken intramuscular in 400 000 units doses 8 times a day within 28 days.

The second course of penicillin treatment in the same doses is prescribed after two weeks interval.

Method 2
Treatment is done in the same way as it was described in the previous method, but instead of soluble penicillin novocaine penicillin salt is used in a dose 600000 units 2 times a day.

Treatment can be also done by procaine penicillin in 1.2 million units doses once a day. Duration of the first course of treatment is 42 days, the second is 14 days.

B. Treatment of patients with late neurosyphilis
Treatment of patients with late neurosyphilis (a progressive paralysis, tabes dorsalis) is done by the same methods recommended for treatment of patients having early neurosyphilis. Distinction

is that instead of one course two treatment courses are prescribed, and spinal fluid control should be done after six months.

In case if SF sanitation is absent then one more treatment course should be done.

Prednisolone usage in the beginning of therapy is prescribed to patients with progressive paralysis who may get the aggravation of psychotic symptoms on the treatment background.

Special attention is paid to the treatment methods concerning cerebrum or spinal cord gummas. This pathology needs prednisolone application together with penicillin therapy which should be done within the first course of treatment (two weeks); it improves treatment's efficacy. Prednisolone treatment may also precede penicillin therapy for few days, what promotes recourse of clinical symptoms of disease.

Duly revealing and adequate treatment of cerebrum and spinal cord gummas may bring complete recovery (SF control and MPT are necessary). A progressive paralysis and tabes dorsalis are most resistant against treatment. As a rule, the best treatment result is the cessation of disease's progress.

9. Alternative (reserve) methods of syphilis treatment

In case of penicilline intolerance so-called reserve preparations are to be used. Doxycycline is a preferable one. It is applied per os in a dose 0.1 twice a day.

Preventive treatment duration is 10 days, primary syphilis treatment duration is 15 days, secondary and early latent syphilis treatment duration is 30 days.

Tetracycline is applied in a daily doze 2.0 (on 0.5 x 4 times a day). It is necessary to pay attention to observance of equal intervals between receptions of a preparation (six hours). Duration of treatment is the same, as in the application of doxycycline.

While taking doxycycline and as well as tetracycline therapy during summertime patients should restrain from long irradiation under direct sun in order to avoid photosensitizing collateral action. Children under eight are not recommended to take tetracycline preparations as they interact with bone tissue.

Pregnant women being not able to take tetracycline preparations should take erythromycin in the same daily and single doses and with the same duration of rates as tetracycline. As erythromycin doesn't penetrate through placenta so the child should be treated with penicillin after his birth.

Besides semisynthetic penicillins, oxacillin, and ampicillin can be applied. They are injected intramuscularly in a dose 1 million units per injection (one dose is dissolved in 5–6 ml of distilled water) 4 times a day. The duration of the preventive treatment is 10 days, the primary syphilis treatment duration is 14 days, the secondary and early latent syphilis treatment duration is 28 days.

Among the preparations of the cefalosporin line ceftriaxone – cefalosporin of the third generation is recommended. It penetrates into organs, tissues and liquids nicely, especially into spinal fluid . It has a high antitreponemal activity. It is significant to consider that the experience

of ceftriaxone therapy is limited nowadays. The following recommendations on its usage have been compiled on a base of few abroad and our own results data.

Ceftriaxon is prescribed in a following way:
Preventive treatment – 0.25 g intramuscular daily, totally 5 injections
Primary syphilis – 0.5 g intramuscular daily, totally 10 injections

For the patients having late latent and neurosyphilis daily dose of the preparation 1.0–2.0 g with one injection is recommended. The therapy lasts 14 days. In severe cases (syphilitic meningoencephalitis, acute generalised meningitis) intravenous usage and increasing of a daily dose up to 4.0 are possible.

Azytromycine is recommended only in case of all other reserve antibiotics intolerance. It should be taken in the conditions of strict clinical and serological control. A daily dose of the preparation for an early syphilis form treatment is 0.5 (per one intake), the treatment duration is 10 days.

10. Specific and preventive treatment of pregnant women
Due to effective and short-term modern techniques of diagnosis and of treatment, syphilis is not a reason for pregnancy interruption nowadays. The decision to keep on or to interrupt pregnancy is taken by woman herself.

A. Specific treatment of pregnant women up to 18 weeks inclusive
Treatment of pregnancy up to the 18th week inclusive is carried out in the same way as common treatment according to the diagnosis, following one of the methods suggested in the present recommendations.

B. Specific treatment of pregnant women at term more than 18weeks

Treatment of the pregnant women with primary syphilis

Method 1
Procaine penicillin in a single doze 1.2 million units daily no. 10 or novocaine salt of penicillin 600 000 units twice a day are to be taken for 10 days.

Method 2
Treatment with sodium salt of penicillin 1 million units intramuscular 4 times a day for 10 days is prescribed.

Treatment of the pregnant women having secondary and early latent syphilis

Method 1
Treatment is carried out with procaine penicillin, 1.2 million units per an injection daily, within 20 days; or with novocaine salt of penicillin, 600 000 units twice a day, for 20 days.

Method 2
Treatment with soluble penicillin (sodium), 1 million units 4 times a day for 20 days.

Preventative treatment of pregnant women
Preventive treatment is prescribed for the women who received treatment before the pregnancy and didn’t achieve complete serology (Wassermann) negativation, as well as for women having

started the treatment while their pregnancy, irrespective of its term. Preventive treatment usually starts after the twentieth week of pregnancy, though if specific treatment was started late, then preventive treatment is carried out directly after specific treatment.

Method 1
Procaine penicillin, 1.2 million units is taken daily, within 10 days; or novocaine salt of penicillin, 600 000 units is taken twice a day, within 10 days.

Method 2
Treatment with sodium salt of benzylpenicillin, 1 million units 4 times day, within 10 days is carried out.

In case of penicillin intolerance semisynthetic penicillins or erythromycine (see "Alternative (reserve) methods of treatment of a syphilis") are prescribed for injection while pregnancy.

11. Children's syphilis treatment and prevention

Preventive treatment of children
In cases if a child delivered to mother who has not been treated from syphilis, or the treatment started late (after the thirty-second week of pregnancy), or absence of serology conversion by the moment of delivery, or mother's serofast, then the child should go through preventive treatment course.

Preventive treatment of the child delivered to an untreated syphilis infected mother is carried out according to any method recommended for inborn syphilis treatment.

Preventive treatment connected with insufficient treatment of mother, positive serologic reactions (RPR, VDRL) by the moment of delivery, or mother's serofast carried out according to one of the following methods:

Method 1
Benzylpenicillin (soduim), 100 000 units per 1 kg of weight is given to the child for 10 days. Daily doze is shared into 6 injections.

Method 2
Penicillin novocaine salt, 50 000 units per 1 kg of weight, divided into 2 injections is injected twice a day with 12 hours interval; or procaine penicillin at the same daily dose is injected one time a day.

Method 3
Treatment with foreign long-lasting preparations of benzathinpenicillin – extencillin or retarpen, in a single dose at the rate of 50 000 units per 1 kg of weight, once a week, totally 2 injections.

In case of penicillin intolerance by the child it is possible to accomplish the treatment by semisynthetic penicillin, keeping duration of treatment same as in case of preventive treatment by soluble penicillin.

The technique of preventive treatment by ceftriaxone hasn't been yet worked out completely. It is known from the literary data, that the treatment is carried out for 10 days, in a daily dose of 50 mg/kg, entered in one injection.

Specific treatment of children diseased with early congenital symptomatic and latent syphilis and, treatment in case if pathology in CSF is absent.

A. Treatment without pathology in liquor

Method 1
Benzylpenicillin (sodium) in a doze of 100 000 units per 1 kg of weight, divided into 6 injections is taken every 4 hours daily, within 14 days.

Method 2
Novocaine salt of benzylpenicillin in a daily doze 50 000 units per 1 kg, divided into 2 injections with an interval of 12 hours is taken twice a day; or procaine penicillin in the same dose is injected daily within 14 days.

Method 3
Carried newborn if having no hypotrophy (weight not less than 2 kg) may be treated with foreign long-lasting penicillin preparations (extencilline, retarpene); one doze is 50 000 units/kg of weight, once a week. The course consists of 3 injections. Each dose is divided into 2 parts and injected in both buttocks.

B. Treatment with liquor pathology or without liquor test

Treatment can be carried out with penicillin and novocaine salts or with procaine penicillin according to the above-mentioned methods (section A, methods 1 and 2).

Lasting penicillin preparations application is not recommended.

In case of benzylpenicillin intolerance it is necessary to use semisynthetic penicillins – oxacilline, ampicilline, in the same daily dosage as soluble penicillin which is divided into four parts and injected intramuscularly four times a day. Duration of treatment is the same, as with benzylpenicillin.

In case of all penicillin group intolerance ceftriaxone application is preferable. The daily dose is of 80–50 mg/kg of weight, treatment duration is 14 days.

Treatment of a late congenital syphilis
Procaine penicillin in a daily dose at the rate of 50 000 units per 1 kg of weight is applied once a day within 28 days; a repeating 14 days course should be done after a two-week interval.

Novocaine salt of penicillin in the same daily dose divided into two injections may also be used. The therapy duration is the same as well.

Method 1
Water-soluble penicillin in a daily dose at the rate of 50 000 units per 1 kg of body weight divided into 6 injections in a day can be applied. The first therapy course lasts 28 days, the second one lasts 14 days and should be done after a two-week interval.

Treatment of acquired syphilis of children
Treatment is carried out according to the treatment methods for adults considering the diagnosis and child's age. It is significant that children under two years of age should not be treated with domestic bicillin, as well as children under eight years should not be treated with tetracycline.

Preventive treatment of children
Same methods and same preparations as for adult treatment are used here, except for domestic bicillines for children under two years, and tetracycline preparations for children under eight years.

12. Clinical and serological control over the end of the treatment
Adults and children who have received preventive treatment after sexual or close household contact with a person having early forms of syphilis, are subjected to unitary clinical serological tests in three months after the treatment.

Patients with primary seronegative syphilis should also be observed for three months.

Patients with early forms of the syphilis, who had positive Wassermann results before treatment, should be subjected to clinical serological control until its complete negativation and after that six more months; two serologic blood testing should be done while then. The duration of clinical and serological control is individual depending on the treatment results.

For patients with late forms of syphilis at whom Wassermann reactions after treatment quite often remains positive, it is stipulated obligatory three years term of clinical and serological control. The decision on removal from the registration or prolongation of the control is accepted individually. During control supervision Wassermann reactions (WR) investigate one time in six months within the second and third year. Specific serology reactions (FTAabs, ELISA, TPHA) are tested once a year.

Patients with neurosyphilis irrespective of its stage should be supervised for three years. Results of treatment are observed considering blood serum tests within the terms which have been mentioned above, and also by obligatory liquor testing on its dynamics. The first liquor control should be done in six months after the treatment. If the sanitation of liquor on cells quantity and serology parameters is absent then one more treatment course should be done (antibiotics are likely to be effective only if pathology is present in liquor)

The further control of spinal liquid condition is done once in six months, within the limits of three years of supervision after a patient has been diagnosed.

Stable liquor normalization even if clinical defect is still present can be a reason to remove a person from registration.

Serofast patients should be under clinical serological control for three years.

Children delivered to syphilis infected mothers but having no congenital syphilis themselves should go through clinical serology control during one year irrespective whether they received preventive treatment or not. The first clinical serology examination is carried out at the age of three months; besides, clinical examination of pediatrist, consultation of neuropathologist, the oculist, the otolaryngologist, serological tests – (Microreaction of precipitation (VDRL type),

Treponema Pallidum Immobilization test, FTAabs) should be done. If then Treponema Pallidum Immobillisation test or FTAabs are negative and clinical investigation haven't revealed pathologic changes then test should be repeated at the age of one year, before getting the child removed from the registration.

If at the age of three months any pathology or positive serological tests have been revealed then test should be repeated in six months at the age of one year.

Children received specific treatment concerning both early and late congenital syphilis should go through clinical serological control following the same principal as the adults concerning their early and late forms of acquired syphilis, accordingly. But this is prescribed only after a child is over one year old.

Children received treatment concerning the acquired syphilis, go through clinical serology control carry out in the same way as the adults.

In case of clinical or serological relapse patients are subject to inspection of therapist, neuropathologist, oculist, otolaryngologist; besides it is expedient to make a spinal puncture. The treatment is carried out following the techniques stipulated for secondary and latent syphilis, with prescription over six months.

13. Serofast (Seroresistance) and additional treatment
Seroresistance is a stable WR (or RPR) positivity preservation after full treatment concerning early stages of syphilis. Serofast (Seroresistance) appears when within one year after the termination of the therapy WR results with treponemal and cardiolipine antigenes or RPR results remain steady positive without the tendency to decrease in reagines titres. In these cases additional treatment is prescribed.

If one year later full treatment WR (or RPR) negativation doesn't occur, but reagines titres decrease (at least four times), or Compliment Bounding Reaction (WR) positivity degree decreases from sharply positive up to poorly positive than these cases are considered as the inhibition of seroreactions conversion is marked, and supervision is continued for six more months. If during this period the Compliment Bounding Reaction (WR) positivity still decreases then supervision can be continued for six more months. In case of no further decrease of Compliment Bounding Reaction positivity additional treatment is prescribed. Thus, additional and, as a rule, unitary treatment is carried out in view of CSR dynamics in the terms of 1–2 years after the first treatment.

Additional treatment should be carried out following the techniques providing high enough level of an antibiotic concentration in a body. Therefore application of soluble penicillin and average lasting preparations is preferable.

Method 1
Treatment is carried out in a hospital by soluble penicillin in a doze 1 million. units 6 times a day within 20 days.

Method 2
Treatment is on an outpatient basis with procaine penicillin 1.2 million units once a day within 20 days or with novocaine of penicillin 600 000 units, twice a day within 20 days.

Method 3
In uncommon cases treatment can be carried out with lasting preparations of penicillin following the techniques recommended for secondary and early latent syphilis.

Method 4
Treatment is carried out with ceftriaxone 1.0 r intramuscularly once in two days totally 10. Treatment concerning seroresistance of children is carried out in a similar way, considering the calculation of a doze according to the age and weight of the child.

Below we have cited the main results of syphilis diseased patients' treatment with the preparations of soluble penicillin (Table 2, page 51) and imported Benzatinpenicilline (Table 3, page 52).

As described in the Russian medical literature, the speed of serological tests conversion is one of the main criteria of syphilis treatment efficiency. Besides, the terms of seroconversion is not strictly defined: from 1–1.5 years at secondary syphilis and 2 years at early latent syphilis. The point is that because the basic diagnostic serological complex were compliment bounding reactions (Vasserman's reaction with cardiolipin and treponemal antigenes + RPR) to judge a degree of three reactions negativation simultaneously was quite difficult. For example, if within two years after the treatment RPR compliment bounding reactions with cardiolipin antigene was negative, and a compliment bounding reactions with treponemal antigene was poorly positive as well then such patient was considered as failure of treatment. Besides, failure of treatment includes concept as serological and clinical relapses.

Previously in the regular researches the RPR titer was not being determined. Only in 2001 the Health Ministry of Russia authorized a new diagnostic complex: RPR (with definition of titer) + TPHA or FTA – abs or ELYSE – on a choice. It has been suggested to consider as seroresistant those cases when the RPR titres decrease less than four times within a year after the end of the treatment *(15)*. Thus, the tool for an objective estimation of syphilis treatment results has just appeared.

It is necessary to specify one more feature of syphilis treatment in Russia: the dose of injected soluble Benzylpenicillin gradually rises. In 1955–1980 the single dose of injected Penicillin was 50 000–75 000 units, since 1981 it was 400 000 units, since 1999 – 1 million units *(2)*. Though the dosage of Russian manufactured long-lasting preparations – Bicillin 1, 3 and 5 does not vary. Increase of single dosages of penicillin is explained by the necessity of its delivery to all the body's compartments with the purpose damage prevention of nervous system, development of seroresistance, and etc.

From the data presented in Table 3 it is clear, that Benzatinpenicillins in the dosages applied in Russian Federation, are effective enough and the treatment results practically do not differ from the results of treatment with soluble Benzylpenicillin (Table 2) which is considered the gold standard. Seroresistance criteria in Benzatynpenicillin usage achieved 25% according to the data presented *(9, 11)*; serological and clinical relapses were 2.5% *(14)*. The experience shows, that if the of supervision period after treatment is increased then the number of seronegative patients increases too and the parameters of efficiency improve. First of all, it concerns the patients with early latent syphilis. For example, in a group of treated patients the number of seropositive patients decreased from 25% up to 10% within four years after the treatment *(12)*.

In the review of basic publications on results of syphilis treatment by preparations of Benzylpenicillin it is described that seroresistance changed from 8% up to 12% *(3,6)* and serological relapse reached 2.8% *(7)*.

Multicentral research of syphilis treatment efficiency has just begun. Randomized controlled trials considered as "the gold standard" of getting of proofs on the efficiency of interventions of public health services in western countries have started to be used by Russian medicine just recently and haven't yet received a wide circulation. In a number of publications on the comparison of treatment methods there are no data on stratification by sex, age, stage of disease. So-called "historical" control, i.e. archives data is being really used. Taking into account, that many researches have not been carried out according to the modern principles of demonstrative medicine, probably, some results are not reliable.

As a positive example of the attempts of comparative study methodical level improvement it is possible to investigate the dissertation of Dr N. Kitaeva *(16)*, who has carried out a retrospective research in comparison of efficiency of treatment of 812 patients (406 patients in each group) with soluble and Benzatinpenicillin in view of the maximal number of factors leveling groups of comparison: age, a sex, prescription of disease, accompanying diseases, a regularity of the control and treatment, etc. Following the Methodical Guidelines of 1999, the patients received treatment with imported Benzatinpenicillins according to the diagnosis, and water-soluble penicillin in 400 000 dose intramuscularly each three hours, following the Methodical Guidelines of 1993. In primary syphilis cases treatment lasted 15 days and in cases of secondary as well as latent syphilis it lasted 28 days.

The received data has testified, that the efficiency of treatment with water-soluble and with lasting penicillin is the same as in cases of primary and secondary syphilis treatment (the distinctions are statistically doubtful) whereas in case of early latent syphilis with the disease duration more than six months the treatment with water-soluble Benzylpenicillin is more effective – failures of treatment have been accordingly 13 and 32 cases *(16, 17)*.

In treatment of syphilis it is necessary to mention the positive results of treatment with Ceftriaxon. In the dissertation it is described that 65 patients with early clinical syphilis had good treatment results *(18)*.

Treatment of HIV-positive patients diseased with syphilis

The number of publications in this field in the Russian medical literature is insignificant. By the present time the guidelines of syphilis treatment of HIV-positive patients hasn't been worked out. They and are not included in the MOH Syphilis Treatment Guidelines either. In some separate messages few data results are cited. They are following below. The data have been collected by the Federal HIV/AIDS Center.

A total of 59 syphilis diseased AIDS-infected patients have been treated according to the following scheme. Benzylpenicillin (natrium salt), 4 million units each 4 hours within 14 days injected intravenously with good results. In case of penicillin intolerance Doxycycline, 0.2 g, 2 times day within 21 days or Tetracycline, 0.5 4 times day within 40 days therapy is prescribed *(19)*.

HIV-positive patients having syphilitic meningitis and hepatitis can be treated in a following way: 4 million units of penicillin are injected intravenously every 4 hours within 14 days; in total 336 800 000 units are prescribed for the course *(20)*.

One patient with syphilitic encephalitis was treated with Benzylpenicillin, 4 million units injected intravenously every 4 hours within 14 days. After 2 weeks the treatment course was repeated *(21)*.

Treatment of Neurosyphilis

Because cases of neurosyphilis are quite rare, the number of publications on it are insignificant.

Treatment of 12 patients with early neurosyphilis (4 patients with asyptomatic meningitis, and 8 patients with meningovascular meningitis) was done with Ceftriaxon (total dosage is 14 grams), 1 g injected IM every day. The effect was quite good: eight patients had eyesight recovery and neurologic symptoms elimination *(22)*.

The retrospective analysis of 25 case notes of patients with neurosyphilis having been observed in psychiatric and neurologic clinics in Moscow in 1995–1996. Five patients received syphilis treatment before, three patients had progressive paralysis, one patient had meningovascular syphilis, one patient had generalized meningitis, twenty patients didn't receive any treatment before, seventeen patients had early neurosyphilis and three patients had late neurosyphilis. The treatment varied: Benzylpenicillin up to 24 million units IM daily; Benzylpenicillin, 20–24 million units intravenously daily (not less than 2 weeks), Oxacillin, Ampicillin *(22)*.

Research on treatment of 33 patients with neurosyphilis (13 men and 20 women) at the age of 17–68 years has been done. The following forms of the syphilis pathology were reviewed: asymptomatic meningitis – five patients, asymptomatic meningitis and uveitis – three patients, uveitis – four patients, acute generalized meningitis – one; meningovascular syphilis: cerebral – eleven patients (an ischemic insult – three patients, an ischemic insult + epileptic syndrome – three patients, epileptic syndrome – one, personality changes (mental disorders) – two patients, meningoneuritis – two patients, spinal meningomyelitis – six patients). The late forms – spinal cord gummas – one patient, a progressive paralysis – two patients. Treatment included: a) (Natrium) Sodium salt of penicillin – 1 million units injected intramuscularly 4 times day + Probenecid 500 mg 4 times daily (30 minutes prior to introduction of penicillin) for the course lasting 14 days – seven patients; b) Sodium salt of penicillin – 2 million units intramuscularly 4 times day + Probenecid on 500 mg 4 times day (30 minutes prior to introduction of penicillin) for the 14 days course – 21 patients; c) Sodium salt of penicillin – 4 million units orally 6 times day (in daily dose 24 million units) for 14–28 days course – five patients; d) Oxacillin, 1 million units per day intramuscularly 4 times day + Probenecid, 500 mg 4 times day (30 minutes prior to introduction Oxacillin): for 28 days course – one patient; and e) Ceftriaxon, 1.0 g intramuscularly once a day for a 10 day course – one patient; the same thing, taken intravenously – one patient. The estimation of efficiency of treatment was carried out, according to two criteria: liquor sanitation and recourse of clinical changes. After one of treatment 50% of the patients had liquors sanitation. 25% of the patients had clinical recovery; 38.8% got significant improvement of health condition. Based on the received results the author concludes that the optimal treponemacide concentration in a cerebral liquid was by injection of sodium salt of penicillin in high doses or by a combination of penicillin injected intramuscularly and Probenecid. The last method is a highly effective and most convenient for neurosyphilis treatment *(24)*.

Syphilis treatment during pregnancy
A research was carried out among 53 pregnant women having syphilis diagnosed while their pregnancy: 20 patients with secondary syphilis and received treatment with 600 thousand units Novocaine salt of Benzylpenicillin, 2 times daily, 16 days; 33 patients with latent syphilis received treatment with Novocaine salt of Benzylpenicillin, 600 thousand units, 2 times daily, 28 days + Theonicol (a preparation raising placenta permeability and promoting increase of concentration of an antibiotic in a blood-groove of a fetus).

Table 4. Dynamics of antibodies titres decreasing before and after the treatment course with Novocaine salt of Benzylpenicillin (during pregnancy)

Test	Secondary Syphilis		Latent syphilis	
	Before tre	After tre	Before tre	After tre
FTA abs	1:752	1:446	1:188	1:130
ELISA	1:2635	1:547	1:2635	1:652
TPHA	1:4333	1:881	1:1813	1:573

The remote results of treatment of 53 women during 6–24 months: no clinical and serological relapses have been revealed. Fifty-five percent of the patients with secondary syphilis had experienced treponemal tests positivity decrease by the end of second year after the treatment. In the clinical serological inspection of 22 children born from the mothers, who had received specific treatment by Novocaine salt of Benzylpenicillin while the pregnancy, no cases of inborn syphilis have been revealed. The placentas inspection has shown their maturity, normal structure, absence of a specific pathology attributes. The normal weight of a body of newborn children was marked. The inspection of the fetuses of nine women having interrupted their pregnancy in the terms of 21–24 weeks (seven women with secondary and two with latent syphilis) has shown, that age of the fetuses, as well as the lung structure, myocardium, liver, spleen, thymus gland, kidney, zone of growth of bones of upper and lower extremities, and inflammation signs absence in the above-stated organs corresponded with the pregnancy terms *(25)*.

One more research study of pregnant women has been carried out. It has aimed to define the necessity of preventive treatment of pregnant women (repeated course of treatment of pregnant women in term of 18–22 weeks of pregnancy, before receiving specific therapy concerning a syphilitic infection while the current pregnancy or before; it is directed on sanitation of a fetus). A total of 132 pregnant women, on term of pregnancy of 8–35 weeks infected with syphilis have been surveyed and treated during their pregnancy. Treatment was carried out with Procaine penicillin and Ceftriaxon. In a control group pregnant women received specific treatment with Procaine penicillin as well as the preventive treatment after 18 weeks of pregnancy. All the children born from the mothers, having received syphilis treatment while the pregnancy, had an acute negative Complex Serology Reactions by the age of 6 months. By the age of nine months their FTA-abs and FTA-200 were also sharply negative *(26)*.

A total of 57 children received Procaine penicillin treatment in a dose of 50 mg per 1 kg of weight, 18 children amongst them had early latent congenital syphilis and 4 children had early congenital syphilis with symptoms. They received 20 days treatment; 28 children with early latent congenital syphilis and 7 children with early congenital syphilis with symptoms received treatment for 14 days. The analysis of results of treatment of children receiving treatment for 20 days and for 14 days hasn’t revealed statistically significant distinctions. After the treatment of

the latent syphilis the seroconversion took place in 6–12 months, statistical significant distinctions of various terms of treatment haven't been received yet *(26)*.

Conclusion

The current treatment methods of various syphilis forms applied in Russian Federation are effective and comparable with methods applied in foreign practice. Moving of a great bulk of patients into outpatient treatment is accessible and acceptable for patients and as well economically advantageous for public health services of the Russian Federation.

Today while development of new Methodical Guidelines of syphilis treatment, the opinions of separate experts without the generalized analytical processing were being mostly counted upon. The doses of the preparations written in the modern western guidelines were raised in comparison with those described.

The Federal AIDS Centre jointly with Dermatovenereology service has been developing guideline of treatment of HIV-positive patients infected with syphilis. In the Methodical Guideline on syphilis treatment issued by the Health Ministry in 1999 the mentioned section is absent, but it is being planned to include it in the subsequent recommendations. The guideline of prevention and treatment of congenital syphilis, syphilis in pregnancy have been worked out by joint efforts of dermatovenereologists and obstetrician gynecologists during the last two years.

Today, the progressive principles of evidence based medicine have gradually been taking root into the practice of drawing up of guideline on diagnostics, treatment and prevention of diseases of the Russian Federation public health services.

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Table 2. Results of treatment of syphilis disease patients with preparations of soluble penicillin

Authors, year	No. of patients	Distribution under diagnoses			Results of the treatment							
					Seroconversion			Seroresistance			Serological relapse	Clinical relapse
		Primary	Secondary	Latent	Primary	Secondary	Latent	Primary	Secondary	Latent		
Zvjagina L.M., et al., 1983 *(3)*	2396	491	1527	378	100%	98.2%	91.8%	–	1.8%	8.2%	–	–
Kotarija V.T., et al., 1985 *(4)*	628	337	291	–	100%	99.4%		–	0.6%		–	–
Glavinskaja T.A., et al., 1985 *(5)*	3132		3132						1.5%		0.03%	–
Borisenko K.K., et al., 1989 *(6)*	370		286	84		91%	75%		2%	11.9%	0.6–1.2%	–
Butovetskij L.D., et al., 1989 *(7)*	341		189	152		97.4%	96.7%		–	–	2.8%	0.5%

Table 3. Results of the treatment of syphilis diseased patients with Benzatinpenicillin

Authors, year	No. of patients	Distribution under diagnoses			Results of the treatment							
					Seroconversion			Seroresistance			Serological relapse	Clinical relapse
		Primary	Secondary	Latent	Primary	Secondary	Latent	Primary	Secondary	Latent		
Mashkillejson A.L., et al., 1997 *(8)*	366	127	156	83	100%	96%					–	–
Petrenko L..A., 1996 *(9)*	346	129	143	74	100%	100%	100%				–	–
Skripkin J.K., et al., 1998 *(10)*	142			142			91.5%			8.5%	–	–
Loseva O.K., et al., 1998 *(11)*	406	50	206	150	100%	92%	93.4%	–	4.8%	4.1%	2.5%	0.28%
Akovbian V.A., et al., 1998 *(12)*	23	183	200	140	100%	99%	91.5%	–	1%	8.5%	0.3%	–
Fedorova L.D., et al., 1998 [13]	140	59	67		100%	100%		–	–		–	–
Chebotarev V.V., et al., 1999 [14]	237	Is not present the data under diagnoses					97.5%			2.5%	0.84%	2.5%

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