Treatment of Syphilis: Current Recommendations, Alternatives, and Continuing Problems

Edward W. Hook III

From the Department of Medicine, The Johns Hopkins University School of Medicine; and the Baltimore City Health Department, Preventive Medicine and Epidemiology, Baltimore, Maryland

Benzathine penicillin continues to be the cornerstone of recommended therapy for syphilis. Recent increases in the syphilis rates in the United States and concerns about the adequacy of currently recommended therapy for syphilis in patients with concomitant human immunodeficiency virus infection have stimulated reappraisal of alternatives to currently recommended therapy. Desirable features of antimicrobial agents for syphilotherapy include long serum half-life, good penetration into the central nervous system, and ease of administration. Benzathine penicillin provides prolonged treponemical levels of penicillin G in serum but does not reliably produce adequate levels of penicillin in the central nervous system. Tetracycline requires multiple daily dosing, has relatively frequent adverse effects, and has unproven efficacy for central nervous system involvement. Erythromycin, which may be less active than tetracycline for syphilis therapy, has similar shortcomings. Recent evaluations of ceftriaxone for early syphilis therapy are promising; however, the optimal dose and duration of therapy are unknown. No currently recommended therapy for syphilis is clearly optimal for reliable, cost-effective therapy. Careful reappraisal of currently available syphilotherapy and alternatives is needed.

Since spirochetal infections may be manifested as acute cutaneous disease at sites of inoculation or as chronic multi-organ systemic illnesses that prominently involve the CNS, it is logical for investigators to suspect that parallels exist with regard to therapy for syphilis and for Lyme disease. Early stages of syphilis or Lyme disease can generally be treated for shorter periods and possibly with lower doses of antimicrobial agents than are required for more established systemic disease. Similarly, in vitro cultivation of Treponema pallidum and Borrelia burgdorferi is difficult and unreliable; thus criteria based on observation of clinical and serologic responses to therapy rather than on eradication of the pathogen must be used to define cure. Finally, in both diseases CNS involvement may necessitate prolonged therapy with high doses of antibiotics that penetrate the CNS to cure established infections. As a result of these parallels, a review of therapy for syphilis may be useful in consideration of therapeutic approaches to patients with Lyme disease. Questions regarding syphilis therapy in patients with diminished cellular immune function due to concomitant infection with human immunodeficiency virus (HIV) may serve to further elucidate critical elements of the therapy for both diseases.

In 1985, for the first time in 5 years, the rates of syphilis in the United States began to rise, and they continue to do so [1, 2]. In 1988, reported rates of primary and secondary syphilis were higher than those for any period in the past 30 years [2]. In the years immediately preceding the resurgence of syphilis, steady declines in national syphilis rates have been attributed primarily to changes in sexual practices by many homosexual men in response to the AIDS epidemic. As increasing syphilis rates became apparent, noteworthy changes in the epidemiology of the disease became apparent as well: rates for homosexual men remained relatively low while rates increased dramatically in heterosexual men and women [2, 3]. At about the same time, concerns were also expressed about the adequacy of recommended syphilis therapy, particularly for patients with concomitant HIV infection [4–6]. Thus, it is timely to review currently recommended therapy for syphilis as well as the suggested alternatives in the context of our present understanding of the disease and of its causative agent, T. pallidum. As is true for all infectious diseases, the discussion of therapy should reflect current knowledge of the biology of the causative agent and the natural history of the disease. Con-
sideration of syphilis in this way, however, is difficult because most descriptions of the natural history of the disease were generated in the pre-antibiotic era and because no major studies of syphilis therapy have been conducted for more than 15 years.

Clinical Staging of Syphilis

For both therapeutic and diagnostic purposes, syphilis is divided into clinically and serologically defined stages [7]. Before they develop serologic reactivity and clinical manifestations, all those patients who have sexual contact with partners with infectious syphilis are referred to as having incubating syphilis, despite the fact that only 30%–50% of those who are untreated will actually develop disease [8–10]. Development of clinical syphilis is usually heralded by the appearance of a chancre, the classical lesion of primary syphilis, at the site of inoculation. Most, but not all, patients with primary syphilis then go on to develop secondary syphilis, a systemic illness characterized by an array of signs and symptoms that may include fever, malaise, generalized lymphadenopathy, and cutaneous or mucosal lesions. Patients with secondary syphilis often also have findings suggestive of CNS involvement such as mild headache or stiff neck. Without treatment, the manifestations of secondary syphilis, like those of primary syphilis, spontaneously resolve over a period of weeks but may recur in up to 25% of patients, usually during the subsequent year. After resolution of the primary and secondary stages, there is a latent period that is further subdivided for therapeutic purposes into latent syphilis of <1 year’s duration (early latent syphilis) and late latent syphilis. About 20%–30% of untreated patients with latent syphilis subsequently develop tertiary manifestations of disease, which may include parenchymatous neurosyphilis, cardiovascular involvement, or gummatous disease at any of a variety of locations. For purposes of treatment neurosyphilis possibly should be considered separately from other manifestations since it may occur at nearly any time in the course of disease and is generally felt to require more aggressive therapy.

In clinical practice there is a substantial overlap in these seemingly discrete stages. Individuals with secondary syphilis often have chancres, and the detection of mucosal or cutaneous secondary manifestations are, at least in part, dependent on the expertise and degree of suspicion of the examiner. Dividing latent syphilis into early and late disease is difficult, and the distinction is somewhat artificial. CNS invasion of T. pallidum occurs in nearly one-third of patients with primary and secondary syphilis [6,11], and neurologic manifestations (including headache, photophobia, other visual or auditory complaints, stroke syndromes, or even the classical manifestations of parenchymal neurosyphilis, tabes dorsalis, or general paresis) may be demonstrable in patients with all stages of disease.

Theoretical Syphilotherapy

The goals of syphilis treatment are twofold: to halt progression of disease in the patient and to terminate the potential infectivity of the patient for his or her sexual partners and, for women, for their offspring. Much of the data on the course of untreated syphilis in humans, upon which our current treatment recommendations are based, were collected before the present era of widespread use of antibiotics. Thus, current therapy for syphilis may not be totally consistent with the disease as it exists today. In addition, therapy effective for normal hosts may not be equally effective for patients with compromised immune function, including patients with concomitant HIV infection [4–6].

Although the clinical stages often overlap and syphilis does not necessarily progress in a simple linear fashion, clinical and serologic staging is still useful for determining dosage and duration of therapy for syphilis patients. Clinical experience has demonstrated that patients with incubating syphilis are much more readily treated than are those with established disease [9,10,12], probably because T. pallidum divides more rapidly in the early stages of disease than in the later stages and, as a consequence, is more susceptible to antibiotic therapy. Similarly, in early (primary, secondary, and early latent) stages of syphilis, the duration of therapy is shorter than that required in the later stages [13–16]. For patients in whom invasion of the CNS has occurred, higher doses of antibiotics may be required to assure adequate levels of drug in CSF, and some antibiotics that penetrate poorly into CSF may not be useful.

In general, parenteral therapy with long-acting benzathine penicillin has been preferred for syphilis therapy in North America for reasons of convenience and because of concerns that suboptimal compliance may contribute to the somewhat higher failure rates in patients receiving multiple-dose, orally ad-
ministered therapy with tetracycline or erythromycin [12]. Multiple oral doses of drugs such as amoxicillin have been suggested as potential treatment alternatives, particularly when neurosyphilis is suspected [17]. Although these regimens are of proven efficacy in compliant patients, they will not be reliable for less compliant patients.

Definitions: Response to Treatment and Treatment Failure

Assessment of response to therapy is based to a minor degree on resolution of clinical signs and symptoms; however, since these tend to be self-limited, the major parameters used to measure response to syphilis therapy are changes in titers determined by quantitative serologic tests for syphilis (e.g., the rapid plasma reagin [RPR] and Venereal Disease Research Laboratory [VDRL] tests). In patients with first episodes of early syphilis, titers can be expected to decline fourfold (two dilutions) within 3 months of therapy and eightfold (three dilutions) by 6 months [18]. In patients with prior syphilis who become reinfected or with late syphilis, the serologic response is often slower [19].

Syphilis therapy may fail for a number of reasons, including use of ineffective medications (such as spectinomycin), use of too little medication (either duration or dose), or (theoretically) antibiotic resistance by T. pallidum. An increase in serologic titer of two or more dilutions may reflect the need for retreatment, as may the failure of serologic titers to show the expected twofold or greater decline following therapy. A number of other factors may indicate the need for retreatment. Persistent or recurrent clinical signs or symptoms following treatment may indicate treatment failure; however, in clinical practice this is uncommon. Although reexposure to a sex partner with untreated syphilis is among the most common indications for retreatment, it cannot truly be considered a treatment failure.

Current Therapeutic Recommendations

The current therapeutic recommendations of the Centers for Disease Control (CDC) [20] clinically and serologically divide syphilis into incubating, early, and late disease, as discussed above. Patients exposed to infectious syphilis but who have yet to develop serologic reactivity or clinical disease (e.g., patients with incubating syphilis) often simultane-

ously acquire other sexually transmitted diseases (STDs) with somewhat shorter incubation periods. In particular, concomitant exposure to syphilis and gonorrhea is not uncommon; thus, whenever possible, gonorrhea should be treated with agents that will also be effective against T. pallidum, if present. As already mentioned, the infecting organism appears to be even more susceptible to antibiotics before the development of primary syphilis than after the appearance of the chancre. This may be part of the reason that single-dose antibiotic therapy for gonorrhea will abort development of syphilis, despite the fact that measurable levels of antibiotic are present for only 18-36 hours. Studies using 2.4 or 4.8 million units of procaine penicillin G [10] indicate that currently recommended gonorrhea therapy with procaine penicillin G (or by extension, ampicillin or amoxicillin) is probably effective for patients with incubating syphilis. Not all drugs recommended for gonorrhea therapy, however, will be effective against incubating syphilis. Studies conducted at the time spectinomycin was initially being evaluated for treatment of gonorrhea demonstrated no significant activity against T. pallidum and that spectinomycin was ineffective for the treatment of incubating syphilis [21]. Although most current gonorrhea therapy appears to be effective for incubating syphilis, preferred treatment is a single im injection of 2.4 million units of benzathine penicillin, a dose that provides treponemical levels of penicillin for at least 2–3 weeks [22].

The currently recommended regimen for treatment of patients with established early (primary, secondary, and early latent) syphilis is a single dose of 2.4 million units of benzathine penicillin G im [20]. For patients with allergy to penicillin, treatment with 500 mg of tetracycline by mouth four times daily for 15 days is recommended [18, 20]. Erythromycin, at the same dose and duration as that recommended for tetracycline, is also listed as alternative therapy; however, comparative studies reported by Schroeter et al. [12] demonstrated higher rates of failure in patients treated with erythromycin than in patients receiving either benzathine penicillin or tetracycline. Close follow-up of all patients with syphilis treated with erythromycin is strongly recommended.

As part of the evaluation of patients with late latent syphilis or syphilis of unknown duration, the CDC guidelines for therapy [20] recommend lumbar puncture to rule out neurosyphilis. A potential limitation of benzathine penicillin for treatment of
late syphilis is its inability to reliably provide treponemidal levels of penicillin in CNS [23–25], a situation that causes concern about the ability of benzathine penicillin to cure patients with neurologic involvement. Persistence of viable T. pallidum in CSF following benzathine penicillin therapy has been demonstrated in patients who have early syphilis with and without coexistent HIV infections, although the frequency with which this occurs is unknown [6, 26]. Logically, patients with persistent T. pallidum in the CNS are at increased risk for relapse and progression to clinical neurosyphilis. Lumbar puncture is therefore recommended for all patients with late syphilis or syphilis of unknown duration to rule out CNS involvement before standard benzathine penicillin treatment is instituted. This will permit more aggressive therapy or at least will indicate the need for closer follow-up of patients with abnormal CSF findings. However, many patients and clinicians alike are unconvinced of the benefit of lumbar puncture when specific symptomatology is absent. As a result, the procedure is not uniformly performed. In the face of conflicting, strongly held opinions and data insufficient to resolve the controversy, debate on the utility of lumbar puncture for directing therapy will continue. It is possible that since CNS involvement by T. pallidum is frequently asymptomatric, some patients with neurosyphilis may be treated with benzathine penicillin regimens of questionable efficacy.

For patients with latent syphilis of unknown duration and for patients with late syphilis other than neurosyphilis (a category that includes latent syphilis of >1 year’s duration and gummatous or cardiovascular tertiary syphilis), the current CDC recommendation is therapy with 2.4 million units of benzathine penicillin administered im once a week for 3 consecutive weeks [20]. It has been suggested that patients in the later stages of disease have more established, relatively slowly progressing disease in which organisms divide at a slower rate, and therefore a longer duration of therapy is needed. Since a single injection of benzathine penicillin provides penicillinemia for 2–3 weeks [22], recommended treatment with three weekly injections of benzathine penicillin does not triple or even double the duration of therapy. Furthermore, because of the relatively low serum levels attained with multiple doses, weekly dosing of benzathine penicillin does not result in levels of drug that are dramatically elevated over the levels attained following a single injection.

For penicillin-allergic patients with late syphilis, the same alternative drugs (tetracycline and erythromycin) and doses (500 mg four times daily) are recommended as for early disease, but the recommended duration is twice as long (30 days) [20]. In these patients, the need for lumbar puncture is more pressing, since the penetration of tetracycline and erythromycin into CSF is relatively poor and these agents are therefore less likely to cure neurosyphilis.

There have been no large studies of therapeutic regimens for neurosyphilis. The current CDC therapy recommendations list either 12–24 million units of aqueous penicillin G iv daily for 10 days followed by three weekly im injections of 2.4 million units of benzathine penicillin or 2.4 million units of aqueous procaine penicillin G im daily plus 500 mg of probenecid orally four times daily both given for 10 days and again followed by three weekly injections of benzathine penicillin [20]. Three weekly injections of 2.4 million units of benzathine penicillin are also listed as treatment for neurosyphilis in the CDC guidelines [20]; however, the efficacy of this regimen has been questioned. A recently convened panel of experts stated that treatment with benzathine penicillin alone was probably insufficient for reliable treatment of neurosyphilis and recommended the deletion of this regimen. An alternative oral therapy for treatment of neurosyphilis—one that has been uniformly effective in limited well-performed studies—consists of 2.0 g of amoxicillin three times daily, plus 500 mg of probenecid twice daily for 10 days [17]. This regimen is likely to be effective for reliable patients who tolerate the high doses of amoxicillin recommended. For patients with a history of allergy to penicillin, the allergy should be verified by skin testing. If allergy is proven, the 30-day tetracycline regimen listed above or the use of a third-generation cephalosporin that penetrates the CNS is probably the treatment of choice, although there are virtually no systematic studies of therapy with either drug.

How successful are the current standard regimens for the treatment of syphilis? Although there are no recent studies, the data from a study of early syphilis begun in the late 1960s provide helpful information [12]. This study compared the efficacy of benzathine penicillin, eight daily doses of procaine penicillin G, or 30 g of tetracycline or erythromycin given over 10 days in patients with primary and secondary syphilis. In the 12 months following treatment, 3.8% of patients treated with eight daily injections of pro-
caine penicillin needed retreatment, and 6 months later no additional patients required further therapy. About 5% of patients treated with the currently recommended benzathine penicillin regimen required retreatment within 12 months, with an additional 2.2% requiring retreatment within the subsequent 6 months, presumably often due to reinfection. When therapy with 30 g of tetracycline given over 10 days was used, the retreatment rates were 9.2% and 12.7% at 12 and 18 months, respectively. The use of 30 g of erythromycin over 10 days resulted in still higher, although not significantly different, retreatment rates — 10.9% and 14.1%, respectively.

Widely quoted studies by Fiumara on the response to syphilis therapy indicate that the rate of serologic response to therapy correlates well with the duration of disease [13–16]. In general, patients with primary syphilis respond more rapidly than patients with secondary syphilis, who in turn respond more rapidly than patients with early or late latent disease. Another report by the same author suggests that patients with prior, adequately treated syphilis who become reinfected often develop higher titers of antibody to T. pallidum and have a delayed serologic response as compared with patients with first infections [19]. An important limitation of these studies, however, was that they reported on patients treated with therapeutic regimens that differed from those recommended by the CDC. In addition, they defined inappropriate clinical responses in all patients treated with ceftriaxone in doses of 2 g im daily for 2 or 5 consecutive days (five and three patients, respectively), as well as in four patients treated with injections of 2.4 million units of benzathine penicillin. In addition, among five patients treated with single 125-mg injection of ceftriaxone, a dose currently used for gonorrhea therapy in several STD clinics [34].

There are also few data regarding alternatives to the presently recommended regimens for treatment of established syphilis. Studies in the late 1960s and early 1970s evaluated the utility of cephaloridine or cephalaxin for syphilis therapy [35–37]. Cephaloridine is no longer commercially available. The studies of cephalaxin utilized 250 mg or 500 mg orally four times daily for 15 days. Four (57%) of seven patients with primary syphilis treated with the 250-mg cephalaxin regimen required retreatment, while none of 13 treated with 500 mg four times daily required retreatment.

More recently, several different dosing regimens of ceftriaxone were evaluated for treatment of patients with early syphilis. Moorthy and co-workers conducted a small comparative study of ceftriaxone for treatment of primary syphilis [38]. They found appropriate clinical responses in all patients treated with ceftriaxone in doses of 2 g im daily for 2 or 5 consecutive days (five and three patients, respectively), as well as in four patients treated with injections of 2.4 million units of benzathine penicillin. In addition, among five patients treated with single 3-g doses, therapy was unsuccessful in one, as indicated by rising VDRL titers. In our own studies [33], 10 patients with primary or secondary syphilis were cured with 250 mg of ceftriaxone administered im daily for 10 consecutive days, as were six patients treated on alternate days with 500 mg for five doses. We have also successfully used ceftriaxone to treat a penicillin-allergic patient with asymptomatic neu-
rosyphilis [39]. Thus, of currently available alternatives for parenteral therapy of syphilis, multiple-dose therapy with ceftriaxone has been the best studied and appears to be effective, although the optimal dose and duration are unclear.

**Continuing Problems in the Management of Syphilis**

As a result of the difficulties associated with sustained in vitro cultivation of *T. pallidum* and the lack of rapid, inexpensive measures for assaying the activity of antimicrobial agents against *T. pallidum* in experimental animals, relatively little is known about the antimicrobial susceptibility of clinical isolates of *T. pallidum*. An interesting method for assaying the in vitro susceptibility of *T. pallidum* that used incorporation of [35S]methionine as an index of inhibition of treponemal protein synthesis was recently described by Stamm and co-workers [40]. These investigators used their assay to test two strains of *T. pallidum*: the Nichols strain, first isolated in 1912 and the laboratory strain from which most current data are derived; and a more recently isolated strain, "street strain 14," which was recovered in 1977 from a penicillin-allergic patient who continued to have treponemes demonstrable in lesions after several weeks of erythromycin therapy. The susceptibilities of these isolates to chloramphenicol, tetracycline, erythromycin, and high and low concentrations of penicillin G were determined. Comparing the activity of these drugs against the two strains of *T. pallidum*, the investigators showed comparable reduction in protein synthesis—as measured by [35S]methionine incorporation—by chloramphenicol, tetracycline, and penicillin. Erythromycin, however, resulted in virtually no inhibition of protein synthesis in street strain 14, although 85%–90% inhibition was seen with the Nichols strain isolates. Thus, this assay has provided in vitro confirmation that street strain 14 treponemes are truly resistant to the activity of erythromycin and is the first clear laboratory demonstration of antibiotic resistance in *T. pallidum*. The method may prove useful for future in vitro studies of the activity of antibiotics that act by inhibition of protein synthesis. How results of this assay may be applied for measurement of antimicrobial susceptibility of treponemes to antibiotics that act by inhibition of cell wall synthesis (e.g., penicillin) or by mechanisms other than protein synthesis remains to be clarified.

Another unresolved question in therapy for syphilis is whether patients with syphilis and concomitant HIV infection require more aggressive therapy than do patients without concomitant HIV infection. On the basis of reports of failure of recommended syphilis therapy in HIV-infected patients, there appears to be a growing consensus that treatment failures are probably more common in these patients and that treatment failure is often manifest as neurosyphilis [4–6]. However, it also appears that most patients with syphilis and HIV infections are successfully treated with currently recommended therapy. Clarification of this question and whether additional diagnostic tests, such as lumbar puncture, should be recommended for HIV-infected patients with syphilis are pressing needs that may be resolved by future studies.

**Conclusion**

While today’s standard therapy for syphilis is successful in many patients, problems still exist with current therapeutic approaches. There is a need for continuing evaluation of alternative agents that may provide solutions to some of the still unresolved issues. The current focus on the relationship between syphilis and HIV infection may provide the incentive for conducting large-scale national studies to evaluate the efficacy of currently recommended and alternative treatments for syphilis in patients with and without HIV infection. Data generated from such studies may be useful in reversing the increasing rates of syphilis occurring in the United States today.

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