Treatment of Syphilis 2001: Nonpregnant Adults

Michael H. Augenbraun
State University of New York–Downstate Medical Center, Brooklyn, New York

After a precipitous increase in the incidence of infectious syphilis in the United States during the late 1980s and early 1990s, the rate of new cases has declined so dramatically that a program initiated by the Centers for Disease Control and Prevention (CDC) to achieve elimination appears to stand a good chance of succeeding. In the fall of 2000, the CDC convened an advisory group to examine the recent medical literature regarding syphilis treatment. Published literature in peer-reviewed journals and abstracts from relevant scientific meetings that have appeared since the last STD Treatment Guidelines meeting in 1997 were reviewed. Where applicable, unpublished data from studies in progress were also discussed. Expert opinion was sought. Through all these efforts, it appears that the azalide azithromycin and the third-generation cephalosporin ceftriaxone should find more definitive roles in the treatment of syphilis. None will eclipse the continued primacy of penicillin for this purpose.

And first th’offending Syphilus was grieved…
He first wore buboes dreadful to the sight,
First felt strange pains and sleepless passed the night:
From him the malady received its name,
The neighboring shepherds caught the spreading flame
At last the city and in court ’twas known.
And seized t’ambitious monarch on his throne.
Girolamo Fracastoro, Syphilis sive morbus Gallicus [1]

According to the Centers for Disease Control and Prevention (CDC), the United States, at the turn of the new millennium, has a unique opportunity to eliminate syphilis within its borders [2]. Such an opportunity has arisen because, for reasons that are somewhat unclear, the incidence of disease is at a historically low level and cases are restricted to specific geographic areas. Additionally, infection with Treponema pallidum remains relatively easy to detect, and treatment of transmissible disease is inexpensive, simple, and effective.

The irony of this current hopeful state of affairs cannot be overstated. Just 10 years ago, rates of syphilis in the United States were at their highest levels since the introduction of penicillin after the Second World War [2]. These high rates were accompanied by reports of unusual and dramatic clinical presentations, as well as the failure of standard therapies in patients coinfected with HIV [3, 4]. In response to these developments, an effort to assess the efficacy of penicillin therapy for syphilis and a search for alternatives recently gained momentum.

At regular intervals, the CDC has published guidelines for the treatment of sexually transmitted diseases [5–9]. These documents have been the result of analyses of the scientific literature and the solicitation of expert opinion. In 2000, another in this series of efforts was...
undertaken. The present article examines the results of that assessment.

MATERIALS AND METHODS

A computerized search on MEDLINE was conducted for articles that related to the natural history and treatment of syphilis published between the end of 1996 (the time of the last comprehensive analysis) through June 2000. In addition, abstracts relevant to syphilis treatment that were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, the International Symposium of Sexually Transmitted Diseases, or the International AIDS Meetings during this same time period were also examined. Data from several ongoing studies, not yet published, were also considered.

With the use of these references, a series of questions was formulated that addressed important aspects of syphilis management. In both the formulation of those questions and the effort to answer them, the opinions of investigators with recognized expertise and interest in syphilis were solicited. When necessary, reference was also made to medical literature that predated the study period. Questions outlined during the last review of this topic also served as a reference [10].

QUESTIONS AND REVIEW OF EVIDENCE

Can azithromycin be considered acceptable therapy for primary- or secondary-stage syphilis? Several properties of the azalide antibiotic azithromycin have long made it an attractive candidate for syphilis therapy. It achieves exceedingly high tissue concentrations and has a very long half-life, important features when considering activity against an organism with a prolonged doubling time like T. pallidum [11]. In vitro and animal model studies have demonstrated that azithromycin is active against syphilis [12, 13]. Verdon et al. [14] published data on the treatment of 16 cases of early syphilis with azithromycin (500 mg orally once daily for 10 days). Thirteen patients completed 6 months of follow-up. Therapy failed in one patient, and the response in another patient whose serological test results declined but did not become nonreactive was considered indeterminate. Hook et al. [15] reported on a prospective study in which 40 individuals exposed to a sexual partner with early syphilis were treated with a single 1 g dose of azithromycin orally while 23 controls received a single dose of standard benzathine penicillin G, 2.4 million U intramuscularly. None of the patients in either group developed syphilis. In another, unpublished, study by the same authors, patients with early-stage syphilis treated with 2 g of azithromycin in a single oral dose were compared with a group treated with azithromycin 2 g given orally once weekly for 2 weeks and another group that received a standard single dose of intramuscular benzathine penicillin, 2.4 million U. Serological and clinical responses were similar in all 3 groups after 3 months (E. Hook, personal communication).

Studies conducted outside the United States have also suggested that azithromycin is effective for the treatment of syphilis. Mashkilleyson et al. [16] described the course of 100 patients with early syphilis who were treated with 1 of 2 azithromycin regimens: 500 mg orally daily for 10 days or 500 mg on alternate days for 11 days. Patients treated with penicillin and erythromycin were included for comparison. The specific time to disappearance of clinical manifestations and the resolution of serological abnormalities in these patients were quantified, although the methods were incompletely described. Despite these shortcomings, clinical and serological evidence of disease resolved within an appropriate amount of time. No signs of tertiary syphilis were seen after 4 years of follow-up. A smaller noncomparative trial of azithromycin was described by Gruber et al. [17]. Serological nonreactivity was achieved after 6 months in 12 (85.7%) of 14 patients with primary, secondary, and early latent syphilis after oral treatment with 1 g of azithromycin followed by 8 days of 500 mg.

Although a large-scale randomized clinical trial of azithromycin versus benzathine penicillin for the treatment of early-stage syphilis could conclusively demonstrate the efficacy of the former, it is unlikely such a study could be completed in the United States given the current low rates of infection. Despite this, sufficient data have accrued that have demonstrated azithromycin's utility for the treatment of early-stage syphilis. As these studies demonstrate, though, there is no consensus regarding a particular dose. Whenever possible, sexually transmitted diseases should be treated with a single therapy. Because some studies have demonstrated that azithromycin can be used in this way, a 1- or 2-g dose once would be reasonable. No studies support the use of azithromycin in the treatment of either latent or tertiary-stage disease.

Can ceftriaxone be used for early- or late-stage syphilis? Ceftriaxone has been proposed as an alternative to penicillin for the treatment of early- and late-stage syphilis (including neurosyphilis) since the late 1980s [18, 19]. Marra et al. [20] attempted to address whether ceftriaxone could be used in the treatment of neurosyphilis in HIV-infected individuals. This was a well-designed prospective, randomized trial. Ceftriaxone at a dose of 2 g intramuscularly once daily for 10 days resulted in CSF responses like those seen with standard doses of intravenous aqueous penicillin G. Unfortunately, few patients were enrolled, and unexpected differences between the groups in each treatment arm limited comparisons. Of interest, despite a lack of well-designed trials supporting ceftriaxone's clinical efficacy for this purpose, a survey of infectious diseases spe-
cular procaine penicillin G would afford weeks of either intravenous aqueous penicillin G or intramuscular benzathine penicillin 2.4 million U at the completion of 2 weeks of therapy would need to be longer than the 10–14 days recommended for neurosyphilis. A single intramuscular injection of benzathine penicillin 2.4 million U at the completion of 2 weeks of either intravenous aqueous penicillin G or intramuscular procaine penicillin G would afford ≥3 weeks of serum penicillin levels. It would be safe and reasonable.

Are there any data to support the use of weekly benzathine treatments after the conclusion of intravenous or intramuscular penicillin therapy for neurosyphilis? No data currently exist to support this practice. From a theoretical standpoint, under the assumption of varying levels of metabolic activity among infecting organisms, it is conceivable that latent infection could coexist with symptomatic or more likely asymptomatic neurosyphilis. In such a circumstance, the duration of therapy would need to be longer than the 10–14 days recommended for neurosyphilis. A single intramuscular injection of benzathine penicillin 2.4 million U at the completion of 2 weeks of either intravenous aqueous penicillin G or intramuscular procaine penicillin G would afford ≥3 weeks of serum penicillin levels. It would be safe and reasonable.

Is there any new evidence to suggest that HIV infection significantly modifies the natural history of syphilis or its response to therapy? Although case reports and small case series over the years have suggested that syphilis is somehow modified with concurrent HIV infection, no well-controlled large-scale study has confirmed this. In 1997, Rolfs et al. [22] reported on the largest cohort of early-stage syphilis studied since the years shortly after the introduction of penicillin. Patients with early-stage syphilis were randomized to receive either a standard single dose of benzathine penicillin or the same medication with high-dose oral amoxicillin and oral probenecid for 10 days. No unusual presentations were noted. Although HIV-infected individuals with primary syphilis had a slower serological response to therapy, there were no overall differences in response to therapy and no treatment failures. Marra et al. [23] studied the response to therapy of CSF abnormalities in a small group of HIV-seropositive and -seronegative patients with syphilis. Over 6 months of follow-up, they found that the former had slower resolution of white blood cells, protein, and CSF-VDRL. They did not demonstrate any treatment failures. Between 1997 and 2000, only 2 additional studies have appeared that have addressed this matter [24, 25]. In both reports, HIV-seropositive patients with syphilis responded appropriately to commonly used therapies.

Should the indications for CSF evaluation be modified? Despite the well-recognized neurotropism of T. pallidum, the circumstances in which a patient with syphilis warrants a CSF evaluation remain unclear. Currently, the CDC recommends that patients with serological evidence of syphilis with neurological or ophthalmic pathology, latent syphilis, and HIV infection and those who demonstrate a failure to respond to therapy with either rising serological titers or titers that fail to decline appropriately over recommended periods of follow-up should have a CSF evaluation. It is also recommended that patients with other manifestations of tertiary syphilis, such as cardiovascular or gummatous syphilis, have a CSF evaluation. Some experts have recommended that “high-titer” latent syphilis (i.e., >1:32) should undergo a spinal tap for CSF evaluation. Previous reviews of the literature did not support this hypothesis, and in 1998 this recommendation was eliminated [9]. An ongoing study of LP results in patients with syphilis has suggested that high titers may predict abnormal CSF (C. Marra, personal communication). These data are preliminary, though, and, until final analyses are performed, it may be premature to make this a formal recommendation again. More vexing perhaps for many clinicians is the clinical situation in which an elderly person with minor cognitive deficits is found to have a reactive serological test for syphilis and either no history or a distant history of treatment. Strict interpretation of the criteria in the current STD treatment guidelines would warrant a CSF evaluation in such cases. The incidence of treatable disease in the patient group is undoubtedly small. There are no recent data to either support or refute this practice.

CONCLUSION

Since the last revision of the CDC STD treatment guidelines in 1998, some data have become available that preliminarily support the role of azithromycin as a clinically acceptable alternative to penicillin for the treatment of early-stage syphilis. Additional data have demonstrated that ceftriaxone is being used in this capacity as well and may have some role in the treatment of neurosyphilis. The nature of all these data, though, fail to make compelling cases that either of these agents can be considered equivalent or superior to standard regimens of either intramuscular or intravenous penicillin G, and they should be considered as alternatives only when penicillin is not an option for therapy.

There are also no new data that clarify the impact HIV infection has on the natural history and response to therapy of syphilis in coinfected individuals. For the time being, therapy considered standard for nonimmunocompromised individuals should remain standard for immunocompromised individuals as well. Of course, to reiterate an old medical maxim, “the absence of evidence does not imply the evidence of absence.” More data and better studies would be helpful. Whether they can be expected in the current environment of low syphilis incidence remains to be seen.

References