Treatment of Syphilis, 1998: Nonpregnant Adults

Michael H. Augenbraun and Robert Rolfs

From the Department of Medicine and Department of Preventive Medicine and Community Health, SUNY Health Science Center at Brooklyn, Brooklyn, New York; and the Office of Public Health Data, Utah Department of Public Health, Salt Lake City, Utah

Questions regarding the appropriate therapy for syphilis remain, despite the many years during which this infection has been subjected to intense scientific scrutiny. In an effort to provide guidance for the development of the 1998 sexually transmitted disease (STD) treatment guidelines of the Centers for Disease Control and Prevention (CDC), these questions were outlined and an effort to answer them was made. Articles relating to syphilis treatment published after the previous revision of the CDC STD treatment guidelines (in 1993) and by the end of 1996 were identified with use of MEDLINE. Abstracts from relevant scientific meetings held during that time were also examined. Reference was also made to older literature, and expert opinion was sought. Conclusions were reached and recommendations were made on the basis of published evidence wherever possible.

A randomly selected 6-month index of the Journal of the American Medical Association from the turn of the century contained nearly 40 entries relating specifically to syphilis, far more than heart disease and cirrhosis entries combined [1]. More recently, in 1995, the Index Medicus listed ~150 references to syphilis [2]. Yet, despite the scrutiny to which syphilis has been subjected, both its natural history and the optimal therapeutic approach continue to defy precise description. In the current era, HIV infection has, to a certain extent, underlined the assumed validity of our models of syphilis staging and of our understanding of the clinical and serological response to therapy.

The Centers for Disease Control and Prevention (CDC) has grappled with some of these issues by periodically (in 1982, 1985, 1989, and 1993) providing guidelines for the treatment of syphilis, as part of its comprehensive Sexually Transmitted Diseases (STD) Treatment Guidelines [3–6]. Recognizing that the state of knowledge of STDs is constantly changing, the CDC initiated a revision of those guidelines in 1997. Specialists with interest and expertise in each of the specific STDs under consideration were asked to prepare analyses of the current literature. These were presented for review to CDC staff members, who offered critiques of the presentation and analysis. A revised analysis was then presented to the CDC staff and a panel of nationally recognized experts in each field.

Efforts were made to conform to an evidence-based approach in making conclusions and finalizing recommendations. These recommendations were then presented to all conference participants for final comment. This article examines the data from which current guideline recommendations and revisions for the treatment of syphilis in nonpregnant adults arose.

Methods

A computerized search on MEDLINE was conducted for articles published from 1993 (the time of the last comprehensive analysis) through the end of 1996 that related to the natural history and treatment of syphilis (table 1). In addition, abstracts relevant to syphilis treatment that were presented at an Interscience Conference on Antimicrobial Agents and Chemotherapy, International Symposium on Sexually Transmitted Diseases, or International AIDS Meeting during the period of 1993–1996 were also examined. Data from a CDC-sponsored multicenter trial published in mid-1997 were included [7].

With use of these references as well as the comprehensive review by Rolfs prepared for the 1993 guidelines revision [20], a series of questions was formulated that addressed the central and often ambiguous areas 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 [21]. Where necessary, reference was made to older literature.

Questions and Review of the Evidence

Is a Single Intramuscular Dosing of 2.4 Million Units of Benzathine Penicillin G Adequate Therapy for Early Stages of Syphilis (i.e., Primary, Secondary, and Early Latent)? Does This Apply to Patients Dually Infected with Syphilis and HIV?

Long-acting preparations of penicillin, such as intramuscular benzathine penicillin G (2.4 million units), have been recommended for several decades for the treatment of early stage syphilis [22–24]. Although the studies that led to their recommendation were problematic because of the nonrandom allocation of patients and a lack of uniform outcomes, 40 years’ clinical experience supports the contention that with regard to healing of lesions, resolution of rash, and improvement of serological markers, the current standard therapy is effective.

Only one study since 1993 has directly addressed the issue of therapy for early stage syphilis in a prospective fashion.

Reprints or correspondence: Dr. M. H. Augenbraun, Box 37 SUNY-HSCB, 450 Clarkson Avenue, Brooklyn, New York 11203 (augenm23@hscbklyn.edu).

Clinical Infectious Diseases 1999;28(Suppl 1):S21–8 © 1999 by the Infectious Diseases Society of America. All rights reserved. 1058-4836/99/2801-0003$03.00
Table 1. Selected references from 1993–1996 relating to the natural history and treatment of syphilis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage of disease</th>
<th>No., type of subjects in study</th>
<th>Therapy</th>
<th>Endpoints</th>
<th>Follow up</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[7]</td>
<td>1st, 2nd latent</td>
<td>553 (19% had HIV); 145 under underwent LP</td>
<td>BPG (2.4 MU) vs. same + high-dose Amox/Prob</td>
<td>Serological, clinical, CSF</td>
<td>At 12 mo (59%, 6 mo; 51%, 12 mo)</td>
<td>No serological differences by therapy (6 mo); difference noted for HIV+ patients with 1st disease. CSF WBC counts higher in HIV+ patients; no difference in Treponema pallidum detection or VDRL test result by HIV status.</td>
<td>Large prospective multicenter study; 14% of HIV– patients showed seroreversion by 12 mo</td>
</tr>
<tr>
<td>[8]</td>
<td>HIV+, with NS (+VDRL)</td>
<td>11</td>
<td>APG (18–24 MU) × 10 d</td>
<td>CSF</td>
<td>At 6 w (11) and 24 w (7)</td>
<td>Two had &gt;2-dilution increase in CSF VDRL titers. T. pallidum not isolated after treatment; no way to predict failure</td>
<td>Small study with short follow-up; not comparative; CSF WBC count did not correlate with VDRL result or failure</td>
</tr>
<tr>
<td>[9]</td>
<td>HIV+, 13; HIV–, 9</td>
<td>APG (12–24 MU) or PPG (2-4 MU) + probenecid for 10–14 d</td>
<td>CSF</td>
<td>CSF analysis repeated at two points after therapy (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>HIV–</td>
<td>193 Enrolled (37% had HIV); 120 followed</td>
<td>BPG (7.2 MU)</td>
<td>Serological</td>
<td>At 6 mo (78%), 12 mo (67%), and 24 mo (50%)</td>
<td>No significant difference between HIV+ and HIV– patients in titer response during follow-up</td>
<td>Large loss to follow-up; initial staging unclear; 60% of HIV– patients did not serorevert after 2 y</td>
</tr>
<tr>
<td>[11]</td>
<td>HIV–</td>
<td>16</td>
<td>Azithromycin (500 mg po q.d. × 10 d)</td>
<td>Serological clinical</td>
<td>At 6 mo (81%)</td>
<td>Seroreversion, 11/13, relapse or reinfection, 1/13; indeterminate, 1/13</td>
<td>Small, noncomparative</td>
</tr>
<tr>
<td>[12]</td>
<td>Latent syphilis</td>
<td>52 (43 LP evaluable); 28% HIV+</td>
<td>NA</td>
<td>CSF findings</td>
<td>NA</td>
<td>None were CSF VDRL+; abnormalities more common in HIV+ patients</td>
<td>Cross-sectional</td>
</tr>
<tr>
<td>[13]</td>
<td>Serological reactivity</td>
<td>64 HIV+, matched controls</td>
<td>Various: HIV+ patients received 7.2 MU BPG</td>
<td>Serological</td>
<td>At 6 mo and 12 mo</td>
<td>No dramatic differences in response</td>
<td>Retrospective, population poorly defined; outcomes unclear; &gt;20% of controls did not have 2-dilution drop in titer after 12 mo</td>
</tr>
<tr>
<td>[14]</td>
<td>Seropositive (mostly latent)</td>
<td>31 HIV+, 19 HIV– (in methadone maintenance program)</td>
<td>Various</td>
<td>Serological, clinical</td>
<td>At median of 11 mo (43 evaluable)</td>
<td>No difference in stage; higher initial titer in HIV+ patients; all patients responded &quot;appropriately&quot;</td>
<td>Prospective, clear design; numbers small; no unusual presentations</td>
</tr>
<tr>
<td>[15]</td>
<td>Latent</td>
<td>58 HIV+</td>
<td>NA</td>
<td>CSF findings (TPHA index)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>1st, 2nd</td>
<td>40 (38% had HIV)</td>
<td>NA</td>
<td>CSF findings</td>
<td>NA</td>
<td>WBC count higher in HIV+ patients; MHA-TP and FTA-ABS reactive in all definite cases and a third of &quot;normal&quot; patients; positive index in 12% of &quot;normals&quot;</td>
<td>Retrospective, cross-sectional, small numbers; no obvious differences. Positive index in 57 definite NS cases</td>
</tr>
<tr>
<td>[17]</td>
<td>NS</td>
<td>46 (52%, HIV+)</td>
<td>NA</td>
<td>CSF, clinical, serological</td>
<td>NA</td>
<td>HIV+ more commonly had systemic illness (22%), eye disease, and CSF parameters</td>
<td>Retrospective, cross-sectional</td>
</tr>
</tbody>
</table>
Rolf et al. compared standard benzathine penicillin G (2.4 million units intramuscularly, given once) to the same regimen plus 2 g of amoxicillin and 500 mg of probenecid (orally three times daily for 10 days) for 553 HIV-seropositive and HIV-seronegative patients with primary, secondary, or early latent syphilis [7]. Slightly more than 50% of patients were available for follow-up through 6 months and 12 months.

There was only one reported clinical failure, involving an HIV-seropositive patient who received standard therapy. Approximately 15% of patients who received treatment with either regimen failed to meet the standard criterion for serological success (a decrease in the nontreponemal serological titer by two dilutions) by as late as 12 months. HIV-seropositive enrollees with primary syphilis were statistically more likely than their HIV-seronegative counterparts to have this serological characteristic.

In the relatively short follow-up period of that study, none of the HIV-seropositive patients experienced the type of dramatic treatment failure that has been reported anecdotally over the past 10 years. Since it is unclear (in this instance) that serological failure clearly correlates with clinical failure and in the absence of any data supporting a more effective therapy, it seems warranted to continue use of the recommended treatment regimen (2.4 million units of benzathine penicillin G intramuscularly) for early syphilis, irrespective of HIV serostatus.

### Are There Potentially Efficacious Alternatives to Benzathine Penicillin in the Treatment of Syphilis?

Rolf et al. [7] examined high-dose amoxicillin in combination with probenecid vs. the standard dose of penicillin as therapy for early syphilis. This oral regimen was selected for its potential to achieve treponemalidal levels in the CSF, not considered possible with the standard regimen [25, 26]. Although the regimens appeared equally efficacious for early stage syphilis, compliance with such a complex oral regimen for 10 days is problematic.

Ceftriaxone has been repeatedly presented as a possible alternative to penicillin in early stage disease [27]. Unfortunately, no data have been contributed to the medical literature since the last revision of the CDC STD Treatment Guidelines in 1993 that either support or refute this drug’s role in this circumstance. The proper dose, duration, and efficacy of ceftriaxone therapy for early syphilis have not been definitively established. On the basis of pharmacokinetics alone, single-dose ceftriaxone cannot be expected to provide adequate therapy for early syphilis [20]. Therefore, if the clinician decides to use ceftriaxone despite the limited evidence, regimens of at least 5–7 days would seem prudent.

The azalide antibiotic azithromycin has many properties that suggest it might be useful as therapy for early stage syphilis. It is active against *Treponema pallidum* in vitro and has been effective in experimental models of syphilis [28, 29]. Although plasma concentration of azithromycin may be nearly unmeasurable, high levels are achievable in tissue. The half-life of the drug is extremely long, and this makes it ideal as therapy against *T. pallidum*, an organism with a prolonged doubling time [30].

Verdon and colleagues treated 16 patients with early stage syphilis with azithromycin (500 mg orally once daily for 10 days) [11]. Compliance with this regimen was good. Clinical cure was documented for 11 of 13 patients who had >3 months’ follow-up. One patient’s treatment may have failed or the patient may have been reinfected, while another, despite declining serological titers, did not serorevert. Other, ongoing studies suggest this antibiotic may be useful for early stage syphilis and may also be efficacious as a single-dose in preventing incubating syphilis among patients treated for other STDs (E. Hook, personal communication). These data are promising, although preliminary. At this time, too few

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage of disease</th>
<th>No., type of subjects in study</th>
<th>Therapy</th>
<th>Endpoints</th>
<th>Follow up</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[18]</td>
<td>All stages</td>
<td>100 HIV+</td>
<td>BPG (7.2 MU); NS therapy as per CDC</td>
<td>CSF, clinical, serological</td>
<td>At mean of 28 mo (56 followed)</td>
<td>BFP rate of 1.7% in patients with HIV (all &lt;1:4); 15% of those who had LP underwent CSF VDRL testing; 18% (all stages) relapsed; multiple relapses with iv penicillin for NS</td>
<td>Retrospective, noncomparative, small numbers</td>
</tr>
<tr>
<td>[19]</td>
<td>All stages (active latent*)</td>
<td>151 HIV+</td>
<td>NA</td>
<td>Serological, clinical</td>
<td>NA</td>
<td>CD4 cell count correlated with stage</td>
<td>Cross-sectional, retrospective, noncomparative</td>
</tr>
</tbody>
</table>

NOTE: Amox = amoxicillin; APG = aqueous penicillin G; BFP = biologic false positive; BPG = benzathine penicillin G; FTA-ABS = fluorescent treponemal antibody-absorbed; HIV = human immunodeficiency virus/syndrome; LP = lumbar puncture; MHA-TP = microhemagglutination Treponema pallidum; MU = million units; NA = not applicable; NS = neurosyphilis; PPG = procaine penicillin G; Prob = probenecid; TPHA = T. pallidum hemagglutination; VDRL = Venereal Diseases Research Laboratory; 1* = primary; 2* = secondary; + = positive; = negative.
patients have been studied for a general recommendation to be made regarding the use of azithromycin in the treatment of syphilis.

**Should the “Early Latent” Designation Be Maintained?**

Serological evidence of syphilis in the absence of clinical signs or symptoms is referred to as latent-stage disease. Early latency has been classically defined as the period of latency during which symptoms of secondary disease might recur. Clinical experience and the recent study of Rolfs et al. suggest that a single intramuscular injection of 2.4 million units of benzathine penicillin G is adequate therapy for this stage of disease [7]. For patients in whom early latent disease can be accurately diagnosed, on the basis of either recent serological conversion or recent exposure to an infectious individual, no current data suggest that additional therapy beyond the currently recommended regimen is necessary. Since treatment for early latent and late latent stages differ, the designation of the former remains useful.

**Is the Use of Benzathine Penicillin G at a Dosage of 2.4 Million Units for Three Weekly Intramuscular Injections Adequate Therapy for Late Latent Syphilis and Latent Syphilis of Unknown Duration? Is this Recommendation Appropriate for Patients Dually Infected with HIV and Syphilis?**

The adequacy of three weekly intramuscular injections of benzathine penicillin G for the treatment of latent syphilis has never been adequately studied. Although it is difficult to ascertain the optimal treatment regimen on the basis of the medical literature, two pathological aspects of disease that appear to differ in early and latent stages of syphilis have been considered important in the devising of strategies. First, spirochetes probably divide more slowly in latent-stage disease than in early stage disease. It has been inferred that eliminating *T. pallidum* in late latent syphilis requires longer exposure to effective antibiotics than might be needed in early stage syphilis. Sequential dosing with intramuscular benzathine penicillin provides continuous low levels of penicillin for 3–4 weeks.

Second, the goal of therapy for latent-stage disease is primarily to eliminate the risk of progression to end-organ damage in the host and not, as in the case of early syphilis, the resolution of infectious lesions. Although this goal is easily achieved in most patients with standard therapy, it is potentially complicated by the sequestration of organisms in areas inaccessible to adequate levels of antibiotics, such as the CNS. Invasion of the CNS by spirochetes occurs frequently and early in the natural history of syphilis [31], but whether and in what circumstances this leads to progression to neurosyphilis has never been clearly defined. Most patients in whom CNS invasion occurs during early syphilis do not develop neurosyphilis even when untreated.

While use of 2.4 million units of benzathine penicillin G every week for 3 weeks does not achieve treponemacidal levels in the CSF, in the pre-HIV era this regimen appeared to be effective in preventing progression of disease. Few instances of neurosyphilis following this therapy were ever noted [32]. The explanation for this seeming contradiction was that an intact immune system played an important role in disease control in the CNS. An incompetent immune response then became the convenient explanation for the sudden flurry of reports in the mid- to late 1980s of HIV-seropositive patients developing CNS complications from syphilis despite the receipt of standard therapy for early stage disease [33, 34].

These reports appeared to suggest that recommended therapies for syphilis were more likely to fail for HIV-infected patients than for non-HIV-infected patients. However, no well-done comparative study has supported this assertion. The majority of HIV-infected patients appear to respond appropriately to recommended therapies. The true nature and magnitude of the risk HIV infection imparts on the natural history and response to therapy for syphilis have not yet been adequately documented.

In the time since the last revision of the STD treatment guidelines, no substantive data have been published that shed light on the efficacy of standard therapy for late latent syphilis or on the natural history and response to therapy of this stage of disease in HIV-infected patients. Malone and colleagues identified a cohort of 100 HIV-infected patients with serologically evident syphilis from among >1,200 HIV-infected U.S. Navy personnel [18]. CSF evaluation and follow-up data were available for only a small subset of this group, and treatment regimens differed. Relapses, mostly serological, were noted among small numbers of patients with early and latent-stage syphilis.

Goeman et al. examined the serological response to therapy in patients with syphilis in a nested cohort of female sex workers enrolled in a cross-sectional study of STD prevalence in Kinshasa, Zaire [10]. Though it was not explicitly stated in the article, most of the subjects probably had latent-stage syphilis, as few cases of symptomatic disease were noted. Serological responses among HIV-infected and non-HIV-infected women were similar. No indication of clinical relapse following standard penicillin therapy was noted. Gourevitch and colleagues studied a small cohort of patients with latent syphilis enrolled in a methadone maintenance program in New York City [14]. In 11 months of follow-up there appeared to be no difference in the rate of acceptable serological responses to standard therapy between HIV-infected and non-HIV-infected patients.

In the final analysis, there is no indication from the literature that three weekly injections of benzathine penicillin is inadequate for truly latent syphilis. Nor is there any indication that the regimen is inadequate when the patient is concurrently infected with HIV and does not have asymptomatic neurosyphilis (see below). The current recommendations for treatment of latent-stage syphilis, specifically late latent syphilis and syphilis of unknown duration, should remain unchanged.
When Should CSF Examination Precede Treatment for Syphilis?

Lumbar puncture and CSF evaluation are not recommended for early stage syphilis. Invasion of the CNS by treponemes early in the course of syphilis occurs frequently. There is a 30%–40% likelihood of CSF abnormalities in primary- and secondary-stage syphilis [31]. This has never been shown to predict progression to neurological complications. Rolfs et al. did not demonstrate that CSF abnormalities in early stage syphilis, although common, were predictive of treatment failure [7]. CSF abnormalities have also been shown to be common in HIV infection in the absence of any discernible pathogen, except perhaps HIV, and are generally not considered predictive of neurological sequelae [35].

The poor predictive value of CSF abnormalities in early stage syphilis with or without HIV infection cannot justify routine lumbar punctures for this patient population. In this setting, CSF evaluation should be reserved for cases of serological and clinical failure or for those with concomitant neurological or ocular symptoms. No recent studies have found otherwise.

The necessity of CSF evaluation in certain cases of latent-stage syphilis is compelling. For many years, a regimen of three weekly intramuscular injections of 2.4 million units of benzathine penicillin G was considered appropriate and adequate therapy for neurosyphilis, thereby providing a measure of security for those receiving treatment for latent disease who had documented or unappreciated asymptomatic neurosyphilis. The failure to demonstrate treponemacidal levels of penicillin in the CSF after administration of benzathine penicillin, as well as anecdotal reports of failure of this regimen, led to the adoption of a more aggressive approach consisting of intravenous aqueous penicillin G or intramuscular procaine penicillin for 10–14 days for treatment of symptomatic or asymptomatic neurosyphilis [32, 36, 37].

The suggestion that therapy for latent syphilis was not adequate for neurosyphilis posed a diagnostic dilemma. In distinction to early stage syphilis, CSF abnormalities in latent-stage disease have been considered more predictive of progression to neurological complications [38]. It therefore became necessary, for therapeutic purposes, to identify any patient with latent disease who had asymptomatic neurosyphilis. This could be done only by lumbar puncture and CSF evaluation. Unfortunately, this was not practical for many facilities offering care for syphilis. Widely applied, this strategy wasn’t clearly cost-effective either [39].

Risk factors that could be used to predict which patients with latent syphilis might also have asymptomatic neurosyphilis would be considered valuable clinical tools. The 1993 CDC treatment guidelines recommended lumbar puncture and CSF examination be performed for patients with late latent syphilis and latent syphilis of unknown duration in the following specific circumstances: neurological or ophthalmic symptoms; syphilitic aortitis, gumma, or iritis; treatment failure (serological or clinical); HIV infection; serum nontreponemal titer of ≥1:32; and nonpenicillin therapy planned.

Neurological, ophthalmic, or psychiatric pathology in the setting of reactive syphilis serology tests strongly suggests the need for CSF evaluation. Treatment failure, suggestive of infection not responsive to standard therapy, warrants the same diagnostic evaluation. The necessity for lumbar puncture in patients with latent disease and a nontreponemal serological test (NTST) titer of ≥1:32 is unproven, although some studies have suggested that patients with neurosyphilis tend to have high NTST titers [40]. The prevalence of neurosyphilis in the population of patients with latent syphilis and titers of ≥1:32 has never been determined. In a study of a small cohort of patients, Carey et al. were unable to demonstrate a correlation between an NTST titer exceeding 1:32 and CSF abnormalities suggestive of neurosyphilis among either HIV-seropositive or HIV-seronegative patients with latent-stage syphilis [12].

The recommendation that evaluation of CSF precede nonpenicillin therapy for patients with latent syphilis was based on the concern that these therapies (i.e., with tetracyclines and macrolides) had no documented or theoretical efficacy against neurosyphilis (unlike a regimen of 7.2 million units of benzathine penicillin G intramuscularly, which clinicians’ experience showed was effective for curing many cases of asymptomatic neurosyphilis). The planned use of a particular therapy is not predictive of asymptomatic neurosyphilis. Therefore, it is difficult to justify a lumbar puncture for every patient with latent syphilis that warrants nonpenicillin therapy.

For patients with latent syphilis and underlying HIV infection, it still seems prudent to recommend a CSF evaluation. Data culled from more than one recent study suggest that at least 10% of HIV-seropositive patients with latent disease will have a reactive CSF-VDRL, a specific marker for neurosyphilis [15, 18, 41]. Whether or not risk can be further stratified by other clinical indicators such as CD4 cell count or the height of the NTST titer remains to be demonstrated.

What Are the Serological Criteria for Treatment Failure?

Assessing the efficacy of therapies for the various stages of syphilis is complicated by the lack of a clearly defined, consistently observed marker of response. Failure of therapy, as demonstrated by recurrence, persistence, or progression of symptoms or by a rising titer, is a dramatic but rare event. Unfortunately, the absence of these findings does not guarantee microbiological cure or the prevention of long-term sequelae.

Without the ability to establish the elimination of a causative organism as a criterion for cure, the clinician is left to follow the rise and fall of the NTST titer to determine if therapy has been successful. While it is clear that the NTST titer rises with activity of infection and declines with proper treatment, it is not at all clear what constitutes an acceptable decline in titer.
The 1993 STD treatment guidelines specified that the absence of a fourfold decline in titer 3 months after therapy for primary or secondary disease identifies individuals at risk for treatment failure. That recommendation was based on data from a reanalysis of an earlier study in which the endpoint was retreatment. The criteria for retreatment in that earlier study were poorly defined [42, 43]. Subsequent studies have consistently demonstrated that anywhere from 15% to 25% of patients will not have a fourfold decrease in titer over the 3-month period and may in fact not have such a drop over a period extended to 6 months or beyond [7, 44]. To date, no study has documented that these patients are at risk for progression of disease.

While it seems prudent to monitor patients clinically and serologically for an extended period of time, there is no clear evidence that they should receive additional courses of therapy or undergo invasive diagnostic studies (i.e., lumbar puncture) within 3 months after therapy if the NTST titer fails to decline fourfold. The frequency of serological follow-up for nontreponemal patients with early stage disease can probably be safely reduced to 6-month intervals.

The serological assessment of response to therapy in patients with latent-stage syphilis is even more problematic than it is for those with early stage disease. Few studies have offered guidance on this matter. In one recent study, ~30% of HIV-seronegative patients with latent syphilis had not had a fourfold drop in the NTST titer by 12 months after therapy [10]. On the contrary, Malone et al. found that of those patients followed-up, 100% of those with early latent disease and 95% of those with late latent disease had a fourfold decrease in titer by 12 months [18].

According to the 1993 CDC STD treatment guidelines, rising titers or the development of clinical symptoms after therapy indicated treatment failure. The finding of initially high titers of ≥1:32 that failed to decline by 12–24 months after therapy was also recommended as a criterion for identifying patients who require evaluation for neurosyphilis and retreatment as necessary. In the absence of any substantive data to either refute or support these recommendations, they should be regarded as reasonable practice.

What is Appropriate Therapy for Neurosyphilis?

The regimen recommended for neurosyphilis in the 1998 STD treatment guidelines is 18–24 million units of aqueous penicillin G intravenously for 10–14 days. An alternative is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either is commonly followed with a regimen of 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks, to achieve a prolonged course of therapy appropriate for latent syphilis.

At one time, the latter regimen of benzathine penicillin G was considered adequate as therapy for neurosyphilis. The reasons for the substitution of intravenous therapy have been discussed above. It was also considered appropriate to treat neurosyphilis with 600,000 units of intramuscular procaine penicillin G (without probenecid) daily for 10 days. As in the case of weekly benzathine penicillin, this regimen fell out of favor as therapy for neurosyphilis after a small number of reports suggested that the disease progressed in some patients with symptomatic neurosyphilis and that CSF abnormalities failed to resolve with this treatment regimen [45, 46]. One study documented that levels of penicillin in the CSF 3 hours after intramuscular administration of 600,000 units of procaine penicillin G were below the detectable limits of the bioassay and were considered nontreponemacidal [47].

The adequacy or inadequacy of these older regimens has not been properly addressed by any recent study. Some experts argue that the studies which resulted in the abandonment of the older treatment regimens for neurosyphilis are difficult to interpret and don’t necessarily apply to patients with asymptomatic neurosyphilis, particularly non-HIV-infected individuals. A number of studies have suggested that even high-dose intravenous penicillin may not reliably cure all neurosyphilis.

In a small observational study, Gordon and colleagues reported that three of seven HIV-seropositive patients failed to respond appropriately to high-dose penicillin therapy for neurosyphilis [8]. Malone et al. reported that 70% of HIV-seropositive patients treated with high-dose penicillin suffered a serological relapse, and among these were patients with documented neurosyphilis [18]. The number of patients studied in either case was small, and no comparisons with HIV-seronegative patients were made.

Marra and colleagues reported on serial CSF studies in a group of HIV-infected and non-HIV-infected patients with neurosyphilis following CDC-recommended therapy [9]. The CSF-VDRL titer decline appeared to be slower in HIV-seropositive patients than in their HIV-seronegative counterparts. The clinical importance of this finding is unclear. Optimal therapy for neurosyphilis, in terms of either duration or dosage, has not been defined. At the very least the data suggest that patients treated for neurosyphilis, especially HIV-seropositive ones, should be followed closely and undergo repeated CSF evaluation after completing therapy.

Repeated courses of therapy should be considered if clinical, serological, or other markers of disease fail to resolve after the period of time designated in the current treatment guidelines. It is also prudent that the total dosage of daily intravenous penicillin be restricted to the upper range of the standard regimen (i.e., 18–24 MU) to avoid confusion and give patients as much medication as is reasonable. Whether asymptomatic neurosyphilis in non-HIV-infected individuals could be treated with smaller doses of intramuscular procaine penicillin G (i.e., 600,000 units to 1.2 million units q.d.) than those currently recommended is unclear. Since untreated neurosyphilis carries the potential for serious consequences and there are no data to support dose reduction, and since the HIV status of patients is
often unknown, it seems appropriate to recommend high-dose intravenous or intramuscular therapy for all patients being treated for neurosyphilis.

There remains a need for effective alternatives to penicillin. The prolonged half-life, adequate CNS penetration, and adequate activity against *T. pallidum* of ceftriaxone suggest that this drug may be an appropriate candidate for consideration [27, 48]. Previous reviews in both humans and animal models suggested that ceftriaxone may not be any more efficacious than high-dose penicillin, however [49, 50].

**Should Penicillin Desensitization be Performed for Potentially Allergic Patients When Minor Determinants Are Not Available?**

Skin testing with major determinants of penicillin allergy will identify 80%--90% of patients at risk for IgE-mediated penicillin allergy, and the addition of minor-determinant testing identifies >99%. The potentially catastrophic effect of an anaphylactic reaction makes testing only with major determinants unacceptable insensitive. If minor determinants are unavailable, a negative test with major determinants alone does not safely eliminate the need for desensitization. These recommendations are unchanged from 1993. No new literature has appeared on this subject.

**Conclusion**

Since the last revision of the CDC STD treatment guidelines, in 1993, some new data have accumulated that fail to support the general trend over preceding years toward more aggressive diagnostic evaluations and therapy for patients with syphilis. Although clinicians continue to suspect that HIV infection complicates the response to syphilis therapy in some patients, the majority of HIV-infected patients appear as likely to respond to therapy as their non-HIV-infected counterparts. Even if such concerns force a reevaluation of current clinical practices, no new therapeutic options have emerged to equal or supplant standard recommended regimens of penicillin. Some noncomparative data suggest that even the most aggressive administration of penicillin, as intravenous therapy for 10–14 days, may fail to cure some cases of documented neurosyphilis.

Reexamination of the previously determined indications for CSF evaluation for patients with syphilis suggests that such an evaluation may not be necessary or prudent in all instances. It should probably be reserved for special cases such as treatment failures, HIV-seropositive individuals with latent disease, and patients with manifestations of late-stage disease such as neurological, ophthalmic, psychiatric, and cardiac disease.

Finally, it appears likely that serological criteria for treatment failure in early stage syphilis can be modified. Fourfold or greater decreases in titer may more reasonably be expected to occur over 6–12 months, rather than the currently recommended 3 months, and serological and clinical reevaluations may be delayed to reflect this.

Our understanding of this complex disease remains imperfect, despite many years of study. At the very least, it can be said that the clinician and patient should cooperate to ensure long-term clinical and serological follow-up and an appropriate response to therapy.

**References**