Ocular syphilis

Anthony J. Aldave, MD,* Julie A. King, MD,† and Emmett T. Cunningham, Jr., MD, PhD, MPH*

Although the annual incidence of primary and secondary syphilis has dropped to the lowest rate recorded, syphilis remains an important cause of ocular disease. Uveitis is the most common ocular manifestation of syphilis in both HIV-positive and HIV-negative patients, and the diagnosis should prompt an analysis of the cerebrospinal fluid to exclude associated neurosyphilis. Newer modalities such as enzyme immunoassays and genomic amplification using the polymerase chain reaction may prove to be useful techniques to detect *Treponema pallidum* in intraocular specimens. The preferred treatment for all stages of syphilis remains parenteral penicillin G, although the preparation, dose, route of administration, and duration of therapy are dictated by the stage of disease and various host factors. All patients diagnosed with ocular syphilis should be tested for HIV, because the presence of a primary genital chancre increases the risk of acquiring or transmitting HIV, and because risk factors for the two diseases are similar. Curr Opin Ophthalmol 2001, 12:433–441

*Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco, California, USA; and †Department of Ophthalmology, Loma Linda University, Loma Linda, California, USA.

Correspondence to Emmett T. Cunningham, Jr., MD, PhD, MPH, Vitreous-Retina-Macula Consultants of New York, 519 East 72nd St., Suite 203, New York, NY 10021, e-mail: emmett_cunningham@yahoo.com

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Abbreviations

CDC	Centers for Disease Control and Prevention
VDRL	Venereal Disease Research Laboratory test for syphilis

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Epidemiology

The last national epidemic of primary and secondary syphilis reached its peak in 1990. Since that time, the annual incidence of primary and secondary syphilis has declined steadily to the lowest annual rate reported in the United States [1,2] (Fig. 1). In 1999, 6,657 cases of primary and secondary syphilis were reported in the United States, an annual incidence of 2.5 cases per 100,000 population. This figure was down 87% from the 50,578 cases reported in 1990, corresponding to an annual incidence of 20.3 cases per 100,000 population [1,2]. Most of this decline is attributed to lower rates of infection in blacks, in whom the rate of infection is still 30 times that of whites. The number of syphilis cases in homosexual men has increased during this time, however [2–5]. The increase in reported cases among men who have sex with men, many of whom are coinfected with HIV, is thought to be related to an increase in high-risk sexual behavior in this era of highly active antiretroviral treatment and to decreased concern over acquiring or transmitting HIV [5–7].

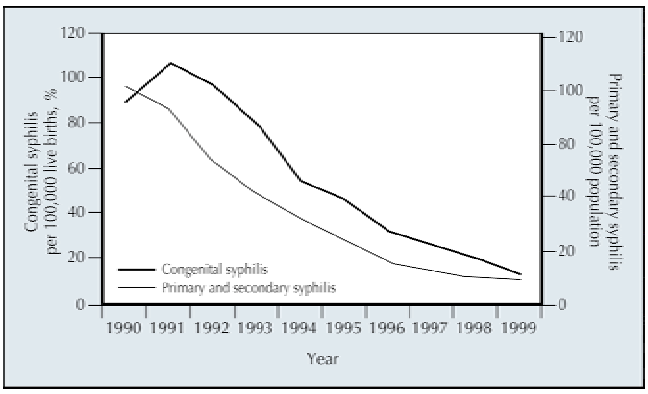
The annual incidence of congenital syphilis, closely related to the incidence of primary and secondary syphilis in the preceding year, also has shown a significant decline over the last decade [8,9]. From 1991 through 1999, the average annual decrease in the rate of congenital syphilis was 22%, to a rate of 14.3 cases per 100,000 live births in 1999 [9]. Most the reported cases, 81%, occurred because the mother failed to receive adequate penicillin treatment before or during pregnancy [8].

To ensure the continued decline in the incidence of primary and secondary syphilis, the U. S. Centers for Disease Control and Prevention recently have launched a National Plan to Eliminate Syphilis from the United States, with the goal of reducing the annual number of primary and secondary cases nationwide to less than 1,000, equal to 0.4 cases per 100,000 population, by the year 2005 [10].

Classification

Syphilis may be transmitted transplacentally to the fetus or acquired postnatally by sexual contact. Congenital syphilis may be divided into an early stage, which develops before age 2 years and corresponds to the secondary stage of acquired syphilis, and a late stage, which develops after age 2 years and is analogous to the tertiary

Figure 1. Incidence of primary and secondary syphilis over time



Since 1990 the annual incidence of both primary and secondary syphilis has declined dramatically in the United States and is now at its lowest reported annual rate.

stage of acquired syphilis. The most common features of early congenital syphilis, appearing several weeks after birth, are mucocutaneous lesions, mainly involving the buttocks and thighs; periostitis; and osteochondritis [11]. Uveitis is the most common ocular complication of early congenital syphilis, with associated chorioretinitis and retinal vasculitis producing a salt-and-pepper pattern of retinal pigmentary mottling [11]. Left untreated, a latent period ensues, characterized by the development of bony and dental abnormalities including frontal bossing, a saddle nose deformity, saber shins, peg-shaped upper central incisors, and abnormal first molars [11]. The most common ocular manifestation of late congenital syphilis is interstitial keratitis, which occurs most frequently between 5 and 20 years of age. Although treatment of affected infants in the first 3 months of life may prevent the development of luetic interstitial keratitis, penicillin administration after this point has no direct effect on the severity or duration of the keratitis [11,12].

Acquired syphilis traditionally has been divided into primary, secondary, latent, and tertiary stages. Primary syphilis is characterized by a chancre, which typically appears 2 to 6 weeks after inoculation with *Treponema pallidum*. This solitary, painless ulcer often is associated with nontender regional lymphadenopathy that may persist for months, although the chancre normally resolves within 3 to 6 weeks [11].

Secondary syphilis develops in almost all untreated patients. The most common sign is a diffuse maculopapular rash, which typically appears approximately 6 weeks after the development of the primary lesion and signifies hematogenous dissemination of *T. pallidum* [13]. Constitutional symptoms such as malaise, fever, sore throat, and arthralgia may accompany the cutaneous eruption [11]. The most common ocular manifestation of secondary syphilis is uveitis [11].

Even without treatment, the signs and symptoms of secondary syphilis tend to resolve in all patients, although relapses may occur in as many as 25% of untreated patients [13]. During the period of early latent syphilis, the first year after infection, relapses are most common, although between relapses, no overt clinical manifestations are noted. The late latent stage may span decades, either remaining stationary or progressing to tertiary syphilis [13].

As in secondary syphilis, uveitis is the most common ocular finding of tertiary syphilis, occurring in approximately 2.5 to 5% of the 30% of untreated patients who progress to this stage [11,13,14]. The most commonly encountered clinical manifestations of tertiary syphilis are cardiovascular complications and neurosyphilis, which may take the form of meningitis, occlusive meningovasculitis, and parenchymatous degeneration including atrophy of the cerebral cortex, optic nerves, and posterior columns of the spinal cord [11].

Clinical features

Known as the great imitator, syphilis may affect all of the structures of the eye (Table 1). Recent publications have highlighted the prevalence and myriad clinical manifestations of syphilitic involvement of the cornea, retina, retinal vasculature, and uveal tract, both in immunocompetent and immunocompromized people.

Interstitial keratitis

In the preantibiotic era, most cases of interstitial keratitis were associated with congenital syphilis. With the widespread use of antibiotics, the prevalence of congenital and acquired syphilis has decreased dramatically, as has the development of syphilitic interstitial keratitis. To determine the most common etiologies of interstitial keratitis at the end of the 20th century, Schwartz *et al.* [15•] reviewed the records of 97 patients diagnosed with interstitial keratitis. Although syphilis remained the most common cause of inactive interstitial keratitis, accounting for 16 (38%) of 42 cases, it was responsible for only 2 (4%) of the 55 cases of active interstitial keratitis. Overall, herpes simplex virus was the most common cause of interstitial keratitis (34 [35%] of 97 cases), including 49% of cases of active interstitial keratitis (27 of 55 cases). Syphilis was the third leading cause of all cases of interstitial keratitis (18 [19%] of 97 cases).

Uveitis

Syphilis was considered a common cause of uveitis in the first half of the 20th century, although, like syphilitic interstitial keratitis, the number of cases of uveitis attributable to syphilis dropped precipitously after the introduction of penicillin [16–18]. Tamesis and Foster [19] found that only 25 (2.45%) of 1,020 new patients seen over a 6-year period at a large uveitis referral center had

Table 1. Ocular manifestations of syphilis

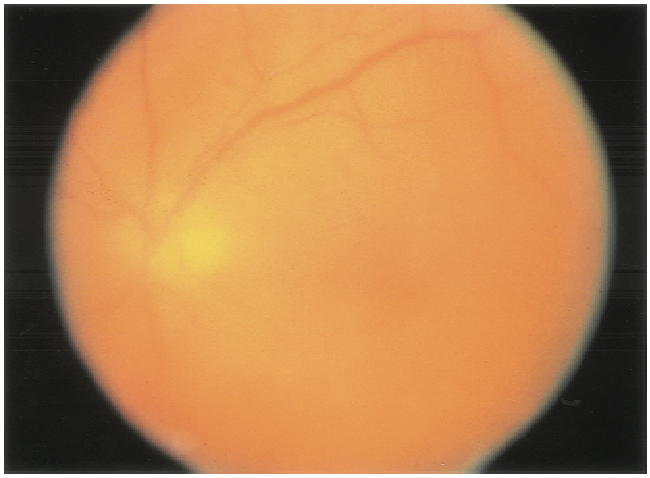
	Stage		
	Congenital	Secondary	Tertiary
Conjunctiva	Mucous patches	Papillary conjunctivitis	Granulomatous conjunctivitis
Sclera	Limbal episcleritis adjacent to IK	Episcleritis	Scleritis
Cornea	Stromal keratitis (80% bilateral)	Marginal corneal infiltrates Keratic precipitates	Stromal keratitis (40% bilateral) Keratic precipitates
Lens	Congenital cataract	Uveitic cataract	Uveitic cataract
Uveal Tract	Acute iritis Secondary cataract or glaucoma Retinal pigmentary mottling in "salt-and-pepper" pattern	Iridocyclitis Vascularized iris nodules (roseola) Isolated vitritis Focal or multifocal chorioretinitis Multifocal choroidal infiltrates	Iridocyclitis Focal or multifocal chorioretinitis Single or multiple gummas
Retina	Retinal vasculitis	Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment CME	Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment CME
Optic Nerve	Optic atrophy	Inflammatory disc edema Papilledema	Inflammatory disc edema Papilledema Optic atrophy Gumma of optic disc
Intraocular Pressure	Ocular hypertension Uveitic glaucoma	Ocular hypertension Uveitic glaucoma	Ocular hypertension Uveitic glaucoma
Pupils			Argyll Robertson pupil
Extraocular Motility		Various cranial nerve palsies	Various cranial nerve palsies

evidence of syphilis. In a review of patients who sought treatment at a uveitis referral center in New York City, Barile and Flynn [20] found that 44 (8%) of 552 consecutive patients seen over a 5-year period demonstrated reactive treponemal antibody assays. In 24 (4.3%) of the 552 patients, syphilis was presumed to be the only cause of the ocular inflammation. The most common manifestations of syphilitic inflammation in these 24 patients were granulomatous iridocyclitis (11 patients, 46%), nongranulomatous iridocyclitis (6 patients, 25%), panuveitis (3 patients, 13%), posterior uveitis (2 patients, 8%), and keratouveitis (2 patients, 8%) [20].

One small case series and two large retrospective series have examined the prevalence and clinical features of and conditions associated with syphilitic uveitis in patients coinfected with HIV. Kuo *et al.* [21] described dense vitritis as the primary manifestation of ocular syphilis in three HIV-infected patients (Fig. 2). Such a dense vitritis in the absence of significant anterior segment inflammation or other signs of posterior uveitis, such as retinitis or retinal vasculitis, is an unusual manifestation of ocular syphilis in both HIV-seropositive and HIV-seronegative patients [21]. In two of the patients, the diagnosis of neurosyphilis led to HIV testing, confirming HIV-seropositivity. All three patients demonstrated reactive nontreponemal antibody titers in the serum and cerebrospinal fluid and were treated for neurosyphilis. Echoing the recommendations of the CDC [22•], the authors advised HIV testing in all patients diagnosed with ocular syphilis [21]. Flood *et al.* [23] reviewed the clinical characteristics of 117 patients with neurosyphilis who were seen in San Francisco hospitals between 1985 and 1992, encompassing the period of the last national epidemic of primary and secondary syphilis. The median age of the patients was 39 years, 91% were male, and 75 (64%) of the patients were HIV-seropositive.

Approximately one third of the patients coinfected with HIV and syphilis were examined for asymptomatic neurosyphilis, and another one third of the patients were

Figure 2. Syphilitic uveitis in HIV-positive patients



Dense vitritis as a presenting sign of syphilis in HIV-infected patients. Reprinted with permission from Kuo *et al.* [21].

examined for symptomatic early neurosyphilis. In the latter group, it was notable that 11 patients (including both HIV-positive and HIV-negative patients), representing 29% of all symptomatic early neurosyphilis patients and 9% of all patients with neurosyphilis, sought treatment for with uveitis [23]. Shalaby *et al.* [24] found that only 13 (0.6%) of 2,085 HIV-positive patients seen in a tertiary uveitis referral center in Baltimore over a 12-year period were diagnosed with syphilitic uveitis. The prevalence of coexistent neurosyphilis was high, however: the cerebrospinal fluid Venereal Disease Research Laboratory test for syphilis (VDRL) was positive in 7 (64%) of the 11 patients tested. Thus, although syphilis does not appear to be a more common cause of uveitis in HIV-infected people than in immunocompetent patients, the frequent association of uveitis with neurosyphilis in HIV-infected patients mandates that cerebrospinal fluid analysis be performed when syphilitic uveitis is diagnosed.

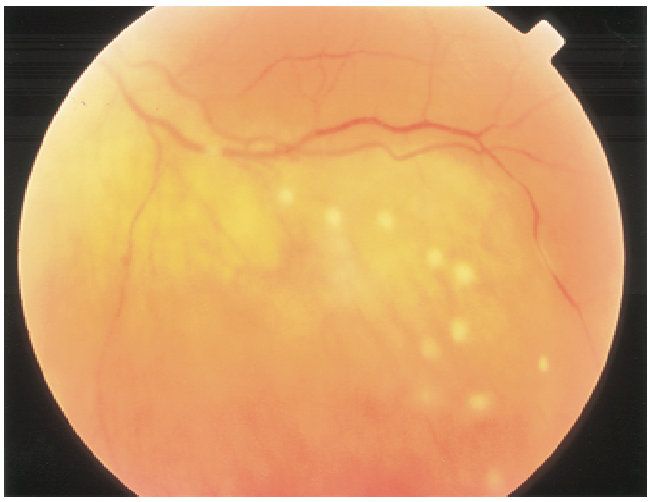
An additional condition associated with syphilitic uveitis is elevated intraocular pressure, as noted by Merayo-Lloves *et al.* [25]. They reviewed the clinical records of 1,254 patients with uveitis seen at a large uveitis center in Boston over a 10-year period. For the purposes of this study, the authors defined secondary glaucoma as pathologic optic disc cupping or a glaucomatous visual field deficit associated with intraocular pressure above 21 mm Hg. One hundred twenty patients with secondary glaucoma were identified (representing 9.6% of all uveitis patients), and etiologies associated with increased intraocular pressure were noted. Fourteen percent of patients with syphilitic uveitis were diagnosed with secondary glaucoma, making syphilitic uveitis one of the leading causes of secondary glaucoma in uveitis patients.

Retinitis and retinal vasculitis

Syphilis may develop in a variety of forms in the posterior segment; therefore, awareness of these protean manifestations is essential to making the correct diagnosis and instituting appropriate therapy. Cubillan *et al.* [26] described a patient with acute peripheral retinal necrosis and vasculitis who was treated initially for acute retinal necrosis syndrome with intravenous acyclovir. Recognition of a distinctive rash on the patient's palms and soles, the demonstration of spirochetes in a silver-stained punch biopsy taken from an area of scalp alopecia, and positive nontreponemal and treponemal antibody titers performed on serum and cerebrospinal fluid established the correct diagnosis [26].

Other manifestations of syphilitic involvement in the posterior segment include focal retinitis, periphlebitis, and, uncommonly, exudative retinal detachment. Jumper *et al.* [27] described three patients with these clinical features who were given incorrect provisional diagnoses before referral, but who were treated correctly after a directed diagnostic evaluation, including treponemal antibody assays, was performed (Fig. 3 and 4). In each case, after treatment with intravenous penicillin for 10 to 14 days, the subretinal fluid resolved.

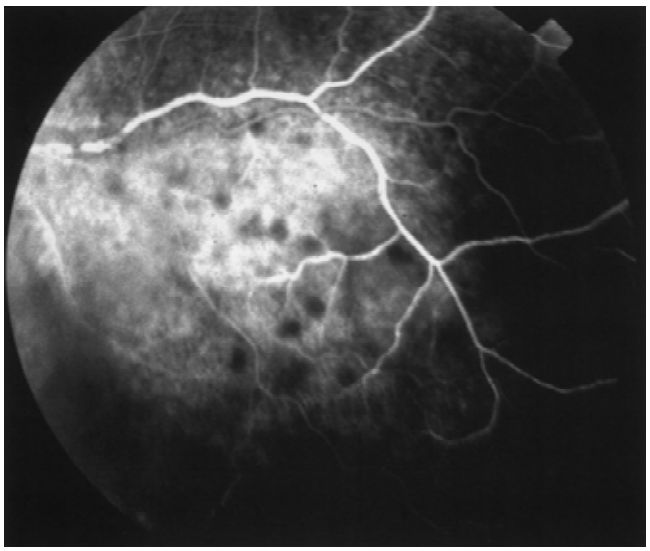
Figure 3. Exudative retinal detachment in a patient with syphilis



Vitritis and serous retinal detachment in a patient with syphilis. Reprinted with permission from Jumper *et al.* [27].

Browning [28•] reported a series of fourteen patients with syphilitic involvement of the posterior segment, examining the relative frequency of clinical findings and

Figure 4. Exudative retinal detachment in a patient with syphilis



Note retinal infiltrates, which show early hypofluorescence on the fluorescein angiogram. Reprinted with permission from Jumper *et al.* [27].

response to neurosyphilis treatment in both immunocompetent patients and those coinfected with HIV (Table 2). All patients responded rapidly to treatment, including the five patients who were HIV-positive. Three of the five HIV-positive patients were diagnosed with routine HIV testing after the serologic diagnosis of syphilis, underscoring the importance of testing for HIV in patients with ocular syphilis.

Villanueva *et al.* [29•] retrospectively reviewed the most common clinical features in a series of patients with syphilitic posterior uveitis. The authors grouped 20 patients into those with acute inflammation, defined as onset less than 3 months before examination (eight patients), and those with chronic inflammation (12 patients). Chorioretinitis was the most common ophthalmologic finding (15 [75%] of 20 patients), followed by panuveitis in three patients (15%) and retinal vasculitis in two patients (10%). Three of the nine patients tested were positive for HIV, although clinical features did not differ between HIV-positive and HIV-negative patients. Poor follow-up limited the interpretation of treatment effect on clinical findings.

Diagnosis

Diagnosis of infection with *T. pallidum* normally is based upon clinical presentation and is supported by serologic testing. Common means of diagnosing other bacterial infections are not possible in the case of syphilis because *T. pallidum* is not visible with Gram stain or by regular light microscopy, and because it cannot be continuously cultured *in vitro*.

Direct examination

Direct microscopic identification of *T. pallidum* is possible using techniques such as darkfield microscopy, silver staining, and immunofluorescence staining. Infectious specimens obtained from a chancre, a mucus patch, or a lymph node aspirate may be examined with one or more of these techniques.

Serodiagnosis

Serologic diagnosis normally is based upon the results of both a nontreponemal test and a treponemal test. Nontreponemal tests such as the VDRL and the rapid plasma reagin (RPR) card test are useful in screening for active disease and antibody quantification. Treponemal tests such as the fluorescent treponemal antibody absorption (FTA-ABS) test, the microhemagglutination-*T. pallidum* (MHA-TA) test, and the *T. pallidum*-particle agglutination test are used for confirmation of previous or current infection. The nontreponemal tests derive their name from the fact that the detected antibodies are directed against mammalian membrane phospholipids such as cardiolipin. These anticardiolipin antibodies may not be detectable in as many as 30% of treated and untreated people during the late latent or tertiary stages of infection [11,19] and may be seen in a sizeable number of patients with diseases unrelated to syphilis (*eg*, collagen vascular disease), underscoring the need for specific treponemal antibody assays in all cases of suspected disease with a negative rapid plasma reagin test or VDRL.

Table 2. Relative frequency of ophthalmic signs in patients with ocular syphilis of the posterior segment

Sign	Eyes (%)
Vitritis	63
Iritis	54
Keratic precipitates	54
Retinitis	54
Vascular sheathing	29
Disc edema	13
Serous retinal detachment	13

N = 24 affected eyes of 14 patients with posterior segment ocular syphilis.
Adapted from [28].

Contrary to the commonly held belief that treponemal antibody assays always remain reactive from the time of infection, various series of patients followed for 1 year after treatment for early syphilis have documented a 5 to 17% rate of transient or persistent seroreversion [30–33]. Treponemal test reversion is unrelated to HIV status or stage of syphilis at diagnosis [30,31]. Although the rate of seroreversion with the (MHA-TA) test was less than that with the fluorescent treponemal antibody absorption test in one series (5% vs. 9% of cases, respectively), the same series found that the (MHA-TA) test was less sensitive than the fluorescent treponemal antibody absorption test in detecting patients with primary syphilis (88.6% vs. 99.2%, respectively) [30]. Because treponemal antibody titers correlate poorly with disease activity, they should not be used to gauge therapeutic response [22•].

Cerebrospinal fluid evaluation

Examination of the cerebrospinal fluid is another means to confirm the diagnosis of *T. pallidum* infection. Cerebrospinal fluid leukocytosis (> 5 white blood cells/μL), elevated protein levels, and a reactive cerebrospinal fluid VDRL each support the diagnosis of neurosyphilis. Unfortunately, the VDRL test to detect the presence of antibodies in the cerebrospinal fluid has low sensitivity; thus, a negative cerebrospinal fluid VDRL does not eliminate the possibility of neurosyphilis.

When to perform a lumbar puncture has been a source of significant debate in the medical literature. Cerebrospinal fluid abnormalities, including the identification of *T. pallidum*, are noted in 23 to 40% of untreated immunocompetent patients with primary and secondary syphilis. Even in the absence of syphilis or other infective pathogens, cerebrospinal fluid abnormalities are common in HIV-positive patients. In neither of these settings, however, is an abnormal cerebrospinal fluid predictive of eventual treatment failure or neurologic complications

[34•,35–37]. Thus, routine cerebrospinal fluid evaluation is not recommended in HIV-positive or HIV-negative patients with early syphilis (*ie*, primary, secondary, early latent) unless one of the following is noted: treatment failure, evidence of central nervous system involvement such as cranial nerve palsies or pupillary dysfunction, or ocular involvement such as uveitis [36].

Patients with latent syphilis of unknown duration and late latent syphilis should undergo cerebrospinal fluid examination if they meet any of the following criteria: neurologic or ophthalmic involvement; syphilitic aortitis or gumma; serologic or clinical treatment failure; HIV infection; a serum nontreponemal titer of greater than 1:32; or use of antibiotics other than penicillin [36]. Whether to perform cerebrospinal fluid analysis in patients with serologic evidence of syphilis and inflammation limited to the anterior segment of the eye is debated. Some physicians will administer penicillin to these patients in neurosyphilis doses without performing a lumbar puncture.

Enzyme immunoassays and polymerase chain reaction-based assays

Limitations of the nontreponemal and treponemal antibody assays have led to the development of improved diagnostic techniques, such as specific enzyme immunoassays and polymerase chain reaction-based DNA amplification strategies. The enzyme immunoassay is being used with increasing frequency in the serologic diagnosis of syphilis because of its suitability for automation and high sensitivity and specificity [38,39]. The highly sensitive technique of polymerase chain reaction amplification has demonstrated the presence of *T. pallidum*-specific DNA in lesions of late secondary and tertiary syphilis where traditional methods have failed to detect the spirochete [40]. The ability to detect *T. pallidum* in minute specimens suggests that polymerase chain reaction may prove a useful approach for testing cerebrospinal fluid and intraocular fluids.

Diagnosis in the HIV-positive patient

Because an increase in the number of syphilis cases has been noted in patients who are coinfected with HIV, each patient diagnosed with syphilis should be tested for HIV as well. Risk factors for acquiring the two diseases are similar, and the presence of a genital chancre increases the risk of acquiring or transmitting HIV [11]. It should be kept in mind that the biologic false-positive rate, the percentage of sera that react in nontreponemal tests but not in confirmatory treponemal tests, is approximately 1% in immunocompetent patients but may be greater in HIV-positive patients [11]. The false-negative rate, defined as the percentage of sera with nonreactive treponemal assays but with specific antibodies against *T. pallidum* antigens, may be greater in HIV-positive patients as well [41].

Treatment

The preferred treatment for all stages of syphilis is parenteral penicillin G. The preparation, dose, route of administration, and duration of therapy are dictated by the stage of disease and various host factors. Treatment recommendations detailed in this section are taken from the CDC's "1998 Guidelines for the Treatment of Sexually Transmitted Diseases" [22•].

Primary, secondary, and early latent syphilis

The recommended treatment regimen for early stages of syphilis remains a single intramuscular administration of 2.4 MU benzathine penicillin G (Table 3). In a prospective, multicenter, randomized trial of 541 HIV-seropositive and HIV-seronegative patients treated for early syphilis with 2.4 MU benzathine penicillin G with or without an additional 10-day course of amoxicillin and probenecid, Rolfs *et al.* [34•] identified only one clini-

Table 3. Treatment of syphilis

Stage	Preferred treatment	Alternative treatment*
Primary, secondary, early latent	Benzathine penicillin G 2.4 million units IM in a single dose	Doxycycline 100 mg po bid × 2 weeks or Tetracycline 500 mg po qid × 2 weeks
Late latent syphilis, latent syphilis of unknown duration†, or tertiary syphilis (without evidence of neurosyphilis)	Benzathine penicillin G 2.4 million units IM administered as 3 doses, given at weekly intervals	Doxycycline 100 mg po bid × 4 weeks or Tetracycline 500 mg po qid × 4 weeks
Neurosyphilis	Aqueous penicillin G 3–4 million units IV every 4 hours × 10–14 days	Procaine penicillin 2.4 million units IM qD × 10–14 days plus Probenecid 500 mg po qid × 10–14 days
Congenital‡	Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days	Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose × 10 days

*See text for patient groups that should undergo desensitization in case of penicillin allergy.
†If clinical evidence suggests tertiary syphilis, CSF examination should be performed.
‡For infants in the first month of life.
Adapted from [22].

cally defined treatment failure. No difference in the rate of clinically or serologically defined treatment failures was noted between the two treatment groups. Additionally, no difference was noted in the rate of clinical improvement between the 101 HIV-positive patients and the HIV-negative patients. However, serologic treatment failures, defined as a decrease in the nontreponemal serologic titer of less than two dilutions 1 year after therapy, were more common among the HIV-infected patients. The authors note that the clinical significance of the difference in serologic responses had not been established [34•].

Late latent syphilis, latent syphilis of unknown duration, and tertiary syphilis without evidence of neurosyphilis

Although no clinical studies to establish the optimal treatment regimen for late latent syphilis have been published, the recommended treatment regimen is three weekly intramuscular administrations of 2.4 MU benzathine penicillin G (Table 3). This recommendation is based in part on the belief that because spirochete replication is slower in the late latent stage than it is in the early latent stage, therapeutic levels of antibiotics must be present for a longer period of time to achieve treponemal eradication in the late latent stage.

Although scattered reports detailing the development of neurosyphilis in HIV-infected patients previously treated with intramuscular benzathine penicillin G for early syphilis exist in the literature [42,43], no well designed clinical trials have substantiated this claim. Therefore, in an HIV-seropositive patient in whom asymptomatic neurosyphilis has been ruled out, there is no convincing evidence that the recommended treatment for late latent syphilis should differ between immunocompetent and immunocompromized patients.

Neurosyphilis

The recommended regimen for treatment of neurosyphilis is 18 to 24 MU aqueous penicillin G intravenously for 10 to 14 days (Table 3). An alternative regimen is 2.4 MU procaine penicillin G intramuscularly daily with 500 mg oral probenecid four times daily for 10 to 14 days. Both regimens are often followed up with three weekly intramuscular administrations of 2.4 MU benzathine penicillin G. All patients being treated for neurosyphilis, especially immunocompromized patients, should undergo serial cerebrospinal fluid analysis with VDRL titers after the completion of therapy.

Whereas most authorities agree that syphilitic retinitis or optic neuritis constitutes neurosyphilis and therefore warrants treatment with intravenous aqueous penicillin G, considerable debate exists regarding the significance of anterior uveitis. Many physicians will treat these patients for presumptive neurosyphilis without performing a lumbar puncture. Others recommend performing serial lumbar punctures in all syphilitic patients with uveitis, retinitis, or optic neuritis, allowing quantification of disease activity, if present, based on the VDRL titers [44].

Congenital syphilis

The recommended treatment for infants in the first month of life is aqueous crystalline penicillin G 100,000 to 150,000 U/kg/d administered as 50,000 U/kg/dose intravenously every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days. An alternative regimen is procaine penicillin G 50,000 U/kg/dose intramuscular in a single daily dose for 10 days (Table 3).

Sexual partners

All persons exposed sexually to a patient with syphilis of any stage should be evaluated clinically and serologically, and given appropriate treatment [22•].

Penicillin-allergic patients

Penicillin remains the antibiotic of choice for syphilis, and no proven alternatives are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. The CDC also recommends using penicillin for treatment of all stages of syphilis in HIV-infected patients [22•]. Doxycycline and tetracycline are alternative treatments for penicillin-allergic patients with primary, secondary, latent, or tertiary syphilis without evidence of neurosyphilis (Table 3). Although antibiotic alternatives such as ceftriaxone and azithromycin have been proposed in patients with a history of penicillin allergy, limited evidence exists regarding the proper dose and duration of therapy [45–47]. Therefore, desensitization is recommended for penicillin-allergic patients in these groups [22•,48].

Role of corticosteroids

A definite role exists for topical, periocular, and systemic corticosteroids in the treatment of syphilitic ocular inflammation. Topical corticosteroids are of proven efficacy in the management of syphilitic interstitial keratitis and anterior uveitis [11]. Oral and intravenous corticosteroids are an appropriate treatment adjunct for posterior uveitis, scleritis, and optic neuritis. Danesh-Meyer *et al.* [48] have recommended the use of corticosteroids before penicillin treatment of patients with neuroophthalmic manifestations of syphilis to avoid the Jarish-Herxheimer reaction (constitutional symptoms secondary to penicillin-induced spirochete death). They recommend pretreatment of patients with 1 or 2 doses of 250 mg intravenous methylprednisolone several hours before the first dose of penicillin, with additional doses given over the first 1 to 2 days of intravenous penicillin therapy.

Evaluating the efficacy of treatment

The traditional measures of success in the treatment of patients with syphilis have been resolution of clinical

disease and demonstration of declining nontreponemal antibody titers. When evaluating the efficacy of treatment in patients with ocular syphilis, similar measures apply: resolution of ocular inflammation; declining serologic nontreponemal antibody titers that return to nonreactive or stable, low titers; and, when applicable, return of cerebrospinal fluid studies to normal. Serial quantitative measurements of the serum nontreponemal antibody titer should be performed at 6, 12, and 24 months after treatment to assess the efficacy of therapy, evidenced by a fourfold reduction in antibody titer, equivalent to a change of two dilutions [22•]. Each measurement should be performed using the same test (rapid plasma reagin test or VDRL) because the rapid plasma reagin titers are often slightly higher than the VDRL titers and therefore are not directly comparable [22•]. The rate of decline of nontreponemal titers is dependent upon a variety of factors, including stage and duration of disease, titer level before therapy, number of previous exposures to *T. pallidum*, and HIV status [34•,44]. If nontreponemal antibody titers fail to decrease fourfold within 6 months after treatment for primary or secondary syphilis, or 12 months after treatment for latent syphilis, clinical and serologic reevaluation should be undertaken (including lumbar puncture), HIV status reevaluated, and retreatment considered [22•]. Approximately 72% of patients with primary syphilis and 56% of patients with secondary syphilis serorevert or demonstrate nonreactive nontreponemal tests 36 months after treatment [49]. Those patients with adequately treated early syphilis who do not serorevert often achieve stable low nontreponemal antibody titers.

In HIV-seropositive patients, quantitative serial nontreponemal antibody titers should be drawn more frequently, at 3, 6, 9, 12, and 24 months after treatment [22•]. The rate of decrease in antibody titer may be delayed in patients with HIV infection, resulting in a greater number of patients who are considered serologic failures and fewer patients who serorevert within 6 or 12 months of treatment. [50]

Analysis of the cerebrospinal fluid should be performed at 6-month intervals to assess the efficacy of therapy, as evidenced by a return of the cell count and protein level to normal, and return of the VDRL titer to nonreactive or a stable, low titer [22•]. If the cell count has not decreased after 6 months or the cerebrospinal fluid has not returned to normal 2 years after therapy, retreatment should be considered [48].

Conclusion

Despite recent, dramatic decreases in the incidence of both acquired and congenital syphilis, syphilis remains an important cause of ocular disease. This is particularly true among HIV-positive patients, where syphilis is the most common bacterial intraocular infection. Frequent ocular manifestations of syphilis include interstitial keratitis, uveitis, retinitis, and retinal vasculitis. Testing of patients suspected of having ocular syphilis should include both a specific treponemal test, such as the FTA-ABS or MHA-TP, and a nontreponemal test, such as the VDRL or RPR, since nontreponemal tests provide added information regarding disease activity, but may be falsely negative in up to 30% of patients. Therapy for ocular syphilis typically involves 10 to 14 day treatment with intravenous penicillin G, 18 to 24 MU daily in four divided doses. All patients with ocular syphilis should be tested for both neurosyphilis and HIV infection.

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