CHAPTER 11

Infectious Uveitis: Bacterial Causes

This chapter includes a related video. Go to www.aao.org/bcscvideo_section09 or scan the QR code in the text to access this content.

Highlights

- Bacterial uveitis most commonly presents as posterior uveitis. Causative organisms include *Treponema pallidum, Mycobacterium tuberculosis,* and less frequently, *Borrelia burgdorferi* and *Bartonella* species.
- Syphilis is reemerging globally and should be considered in the differential diagnosis of any intraocular inflammatory disease.
- Tuberculosis-associated uveitis can arise in the absence of detectable active systemic disease, and the diagnosis is presumptive in most cases.
- Ocular involvement occurs in 5%–10% of individuals with cat-scratch disease (bartonellosis) and may manifest as neuroretinitis, focal/multifocal retinitis, and less frequently, Parinaud oculoglandular syndrome.

Syphilis

Syphilis is a reemerging multisystem, chronic bacterial infection caused by the spirochete *Treponema pallidum.* Transmission occurs most often through sexual contact, but transplacental infection of the fetus is also possible, mainly after the 10th week of pregnancy. In the United States, the infection reached an all-time low in 2000; since then, however, the incidence rates of all stages of syphilis have been increasing among men (particularly those who have sex with men), as well as among women. This rise is associated with an almost twofold increase in the incidence of congenital syphilis in the United States (from 9.4 to 15.7 per 100,000 live births).

Ocular manifestations of both the congenital and acquired forms of syphilis are numerous. Although syphilis is thought to be responsible for less than 2% of all uveitis cases, it is one of the great masqueraders in medicine and should always be considered in the differential diagnosis of any intraocular inflammatory disease. Also, syphilitic uveitis is one of the few forms of uveitis that can be cured with appropriate antimicrobial therapy, even in patients with HIV coinfection. Delay in the diagnosis of syphilitic uveitis may lead to

permanent vision loss as well as substantial neurologic and cardiac morbidity, which early treatment may prevent. See BCSC Section 1, *Update on General Medicine,* for additional discussion of the systemic aspects of syphilis.

Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2021.* US Dept of Health and Human Services. Accessed November 8, 2023. www.cdc.gov/std/statistics/2021/default.htm

Congenital Syphilis

The prevalence of congenital syphilis is increasing in the United States in parallel with higher rates of infection in young women. The increased prevalence is associated with limited, late, or no prenatal care, without serologic screening for the infection. Maternal primary or secondary syphilis is more likely to be transmitted to the fetus than latent syphilis (see the section Acquired Syphilis for discussion of the stages of syphilis); maternal-fetal transmission becomes less likely as the duration of maternal infection increases. See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for additional information on congenital syphilis.

Ocular signs of congenital syphilis may present at birth or decades later. Manifestations include congenital cataract, uveitis, interstitial keratitis, optic neuritis, and glaucoma. In early congenital infection, the most frequent form of uveitis is multifocal chorioretinitis followed by retinal vasculitis. Both may result in a bilateral salt-and-pepper retinopathy that can affect the peripheral retina, posterior pole, or even a single quadrant. The retinopathy is not progressive, and the patient may have normal visual acuity. Less often, there may be a bilateral secondary degeneration of the retinal pigment epithelium (RPE) that can mimic retinitis pigmentosa, with narrowing of the retinal and choroidal vessels, optic disc pallor with sharp margins, and variable deposits of pigment.

The most common ocular sign of untreated late congenital syphilis is nonulcerative stromal interstitial keratitis, which occurs in up to 50% of cases, most commonly in girls (Fig 11-1). The constellation of interstitial keratitis, cranial nerve VIII deafness, and Hutchinson teeth is called the *Hutchinson triad.* Interstitial keratitis may also be accompanied by anterior uveitis that occurs in response to *T pallidum* in the cornea (keratouveitis). Symptoms include intense pain and photophobia. Blood vessels can invade the cornea, and late stages show deep "ghost" (nonperfused) stromal vessels and corneal opacities. If untreated, the corneal inflammation may resolve, but residual focal or diffuse corneal opacification or scarring can cause severe vision loss. Anterior uveitis accompanying interstitial keratitis may be difficult to visualize because of corneal haze. Glaucoma may also occur. For further discussion of interstitial keratitis, see BCSC Section 8, *External Disease and Cornea.*

Acquired Syphilis

Primary syphilis

Primary syphilis follows an incubation period of approximately 3 weeks and is characterized by a *chancre,* a painless, solitary lesion that originates at the site of inoculation. The chancre heals spontaneously, and signs of dissemination appear after a variable quiescent

period of several weeks to months. The central nervous system (CNS) may be seeded with treponemes during this period, often in the absence of neurologic findings.

Secondary syphilis

Secondary syphilis occurs 6–8 weeks after resolution of the chancre and is heralded by the appearance of lymphadenopathy and a generalized maculopapular rash (Fig 11-2) that may be prominent on the palms and soles. Uveitis occurs in approximately 10% of cases. This stage is followed by a latent period, occurring within 1 year of infection (early latency) to decades later (late latency).

Tertiary syphilis

Approximately one-third of untreated patients develop tertiary syphilis, which may be further subcategorized as *benign tertiary syphilis* (the characteristic lesion is a gumma, most frequently found on the skin and mucous membranes but also in the choroid and iris), *cardiovascular syphilis,* and *neurosyphilis.* Although uveitis may occur in up to 5% of patients whose disease has progressed to tertiary syphilis, it can occur at any stage of infection, including primary

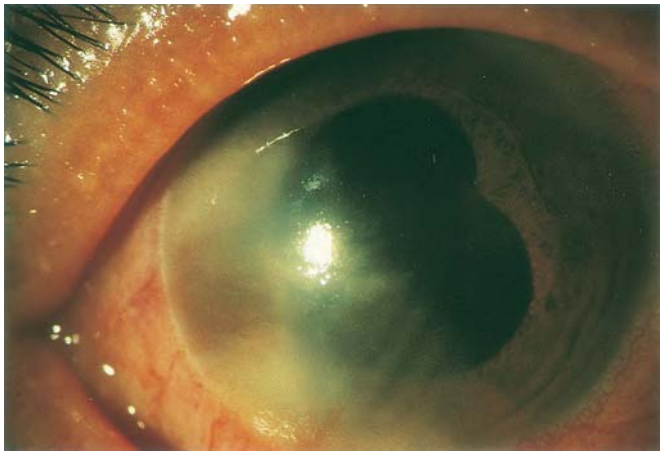

Figure 11-1 Ocular syphilis. Active syphilitic interstitial keratitis.

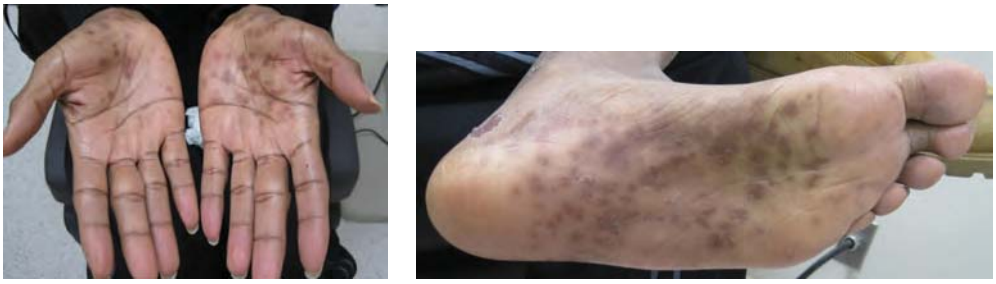

Figure 11-2 Syphilis. A characteristic maculopapular rash on the palms and soles of a patient diagnosed with syphilis. *(Courtesy of Wendy M. Smith, MD/National Eye Institute.)*

disease. Because the eye is an extension of the CNS, ocular syphilis is considered a manifestation of neurosyphilis, a concept that has important diagnostic and therapeutic implications.

Ocular involvement

Ocular manifestations of acquired syphilis are protean, and any structure of the eye (including conjunctiva, sclera, cornea, lens, uvea, retina, and optic nerve), as well as the cranial nerves and pupillomotor pathways, can be involved. Patients may present with pain, redness, photophobia, blurred vision, and floaters. Intraocular inflammation may be granulomatous or nongranulomatous, unilateral or bilateral, and it may affect anterior or posterior segment structures. Anterior segment findings can include iris roseola, vascularized papules (iris papulosa), large red nodules (iris nodosa), and gummata. Interstitial keratitis, posterior synechiae, lens dislocation, and iris atrophy may also occur.

Posterior segment findings of acquired syphilis include vitritis, chorioretinitis, focal or multifocal retinitis, necrotizing retinochoroiditis, retinal vasculitis, exudative retinal detachment, isolated papillitis, and neuroretinitis. The most common manifestation is focal or multifocal chorioretinitis, usually associated with a variable degree of vitritis (Fig 11-3). Typically, the lesions are small and grayish yellow and are located in the postequatorial fundus; however, they may become confluent. Retinal vasculitis, optic disc edema, and serous retinal detachment, with exudates appearing around the disc and the retinal arterioles, may accompany the chorioretinitis.

The clinical appearance and angiographic characteristics of syphilitic posterior placoid chorioretinitis are essentially pathognomonic for secondary syphilis (Fig 11-4, Video 11-1). Findings include placoid, yellowish-gray lesions at the level of the RPE, often with accompanying vitritis. The lesions may be solitary or multifocal, macular or papillary. Characteristics of posterior placoid chorioretinitis on multimodal imaging include the following:

- *Fundus autofluorescence (FAF).* The lesions are hyperautofluorescent.
- *Fluorescein angiography (FA).* Lesions show early hypofluorescence and late staining, with retinal perivenous staining.
- *Indocyanine green angiography (ICGA).* Lesions are hypofluorescent.
- *Optical coherence tomography (OCT).* Images show irregularities at the level of the RPE, disorganization, and loss of outer retinal layers.

VIDEO 11-1 SD-OCT of syphilitic posterior placoid chorioretinitis.
Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.

Less common posterior segment findings include focal retinitis, periphlebitis, and, infrequently, exudative retinal detachment. Syphilis may present as a focal retinitis or as a peripheral necrotizing retinochoroiditis that may resemble acute retinal necrosis or progressive outer retinal necrosis (Fig 11-5). Although the foci of retinitis may become confluent and are frequently associated with retinal vasculitis, syphilitic retinitis progresses more slowly than retinitis in acute retinal necrosis and responds dramatically to therapy with intravenous penicillin, often with a good visual outcome. Distinctive punctate inner retinal infiltrates have also been observed (Fig 11-6). Isolated retinal vasculitis that affects the retinal arterioles, capillaries, and larger arteries or veins (or both) is another feature of syphilitic

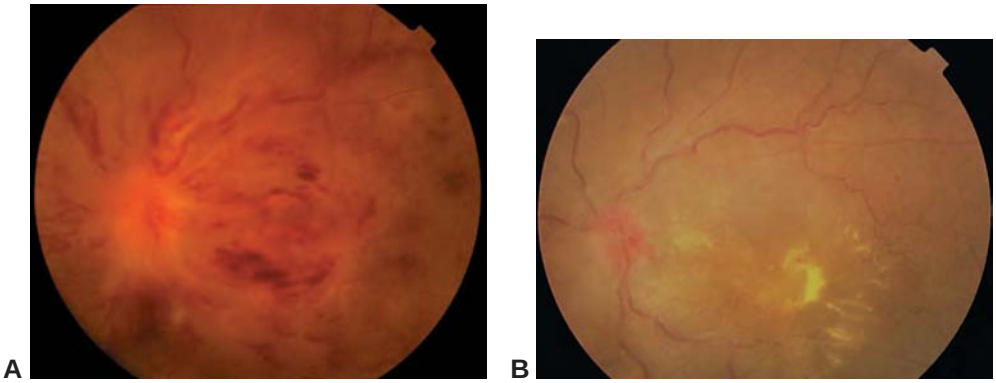

Figure 11-3 Syphilitic chorioretinitis. **A,** Fundus photograph of acute syphilitic chorioretinitis. Note the extensive involvement of the optic disc, retina, and choroid in the posterior pole. **B,** Fundus photograph showing chorioretinitis after 2 weeks of intravenous penicillin therapy. Note the subretinal hard exudate that is organizing, as well as the reduction in disc edema and choroidal inflammation. *(Courtesy of Ramana S. Moorthy, MD.)*

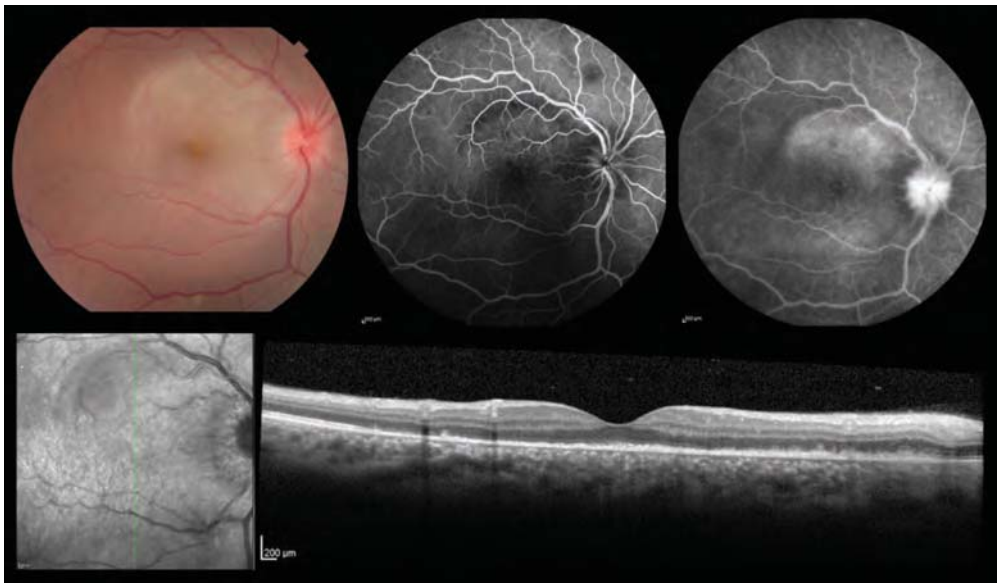

Figure 11-4 Features of syphilitic posterior placoid chorioretinitis on multimodal imaging. Fundus photograph *(top left),* fluorescein angiography (FA; *top middle and top right*), and spectral-domain optical coherence tomography (SD-OCT; *bottom*). Progressive placoid hyperfluorescence is seen on FA *(top right),* corresponding to the yellowish geographic infiltrate in the posterior pole *(top left).* SD-OCT reveals deep granular changes, with disruption of outer retinal layers and underlying homogeneous hyperreflectivity of the inner choroid. *(Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.)*

intraocular inflammation and may best be appreciated on FA. Focal retinal vasculitis may masquerade as a branch retinal vein and/or arterial occlusion.

Neuro-ophthalmic manifestations of syphilis, including the Argyll Robertson pupil, ocular motor nerve palsies, optic neuropathy, and retrobulbar optic neuritis, appear most frequently

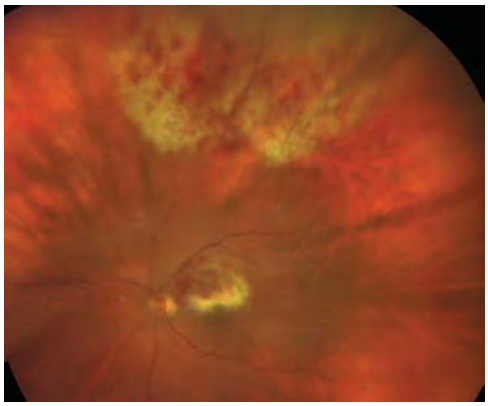

Figure 11-5 Acute syphilitic retinitis. Fundus photograph shows retinal hemorrhages and infiltrates. *(Courtesy of Gaurav K. Shah, MD.)*

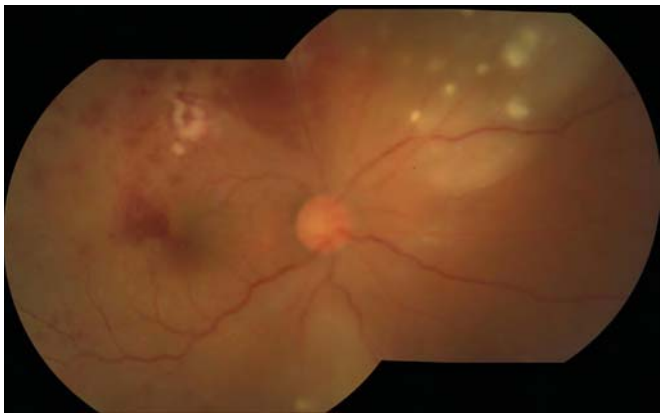

Figure 11-6 Syphilitic posterior uveitis. Fundus photograph reveals punctate inner retinal infiltrates overlying an area of retinal edema superonasally. *(Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.)*

in patients with tertiary syphilis or neurosyphilis. Syphilis is an important entity to consider in the differential diagnosis of patients with neuroretinitis and papillitis who present with macular star formation. See BCSC Section 5, *Neuro-Ophthalmology,* for further discussion.

Immunocompromised patients with syphilis may present with atypical ocular disease patterns. Optic neuritis and neuroretinitis are more common as the initial presentation in these patients, and disease recurrences may be noted even after appropriate antibacterial therapy.

Eandi CM, Neri P, Adelman RA, Yannuzzi LA, Cunningham ET Jr; International Syphilis Study Group. Acute syphilitic posterior placoid chorioretinitis: report of a case series and comprehensive review of the literature. *Retina.* 2012;32(9):1915–1941.

Furtado JM, Simões M, Vasconcelos-Santos D, et al. Ocular syphilis. *Surv Ophthalmol.* 2022;67(2):440–462.

Jumper JM, Randhawa S. Imaging syphilis uveitis. *Int Ophthalmol Clin.* 2012;52(4):121–129.

Rasoldier V, Gueudry J, Chapuzet C, et al. Early symptomatic neurosyphilis and ocular syphilis: a comparative study between HIV-positive and HIV-negative patients. *Infect Dis Now.* 2021;51(4):351–356.

Diagnosis

The diagnosis of syphilitic uveitis is supported by the history and clinical presentation and confirmed by results of serologic testing. Recently, the Standardization of Uveitis Nomenclature (SUN) Working Group defined diagnostic criteria for ocular syphilis that incorporate characteristic ocular findings with serologic evidence.

According to the US Centers for Disease Control and Prevention (CDC), newly diagnosed syphilis cases should be reported to public health authorities according to local regulations. Public health departments can help identify sexual contacts of the patient who are at risk for acquiring and transmitting the disease. All patients diagnosed with syphilis should receive HIV testing because there is a high frequency of coinfection.

Standardization of Uveitis Nomenclature (SUN) Working Group. Classification criteria for syphilitic uveitis. *Am J Ophthalmol.* 2021;228:182–191.

Van Gelder RN. Diagnostic testing in uveitis. *Focal Points: Clinical Modules for Ophthalmologists.* American Academy of Ophthalmology; 2013, module 4.

Nontreponemal and treponemal antigen tests

There are 2 types of serologic tests for syphilis: nontreponemal and treponemal (Table 11-1). Nontreponemal tests (eg, rapid plasma reagin [RPR], VDRL) detect antibodies against host and bacterial lipoidal antigens released during infection. Treponemal tests (eg, fluorescent treponemal antibody absorption [FTA-ABS], syphilis immunoglobulin [Ig] G) detect antibodies against proteins specific to *T pallidum*. The traditional testing sequence starts with a nontreponemal test followed by confirmatory treponemal tests. Recently, treponemal immunoassays have become the preferred initial test because of their improved speed and automated testing and their ability to detect disease in early or latent stages. This testing strategy is called the *reverse sequence syphilis screening algorithm.* Treponemal tests have a higher positive predictive value in patients with uveitis and should be used in conjunction with nontreponemal tests to diagnose ocular syphilis. Treponemal IgG kits are available commercially for home use in the United States.

Nontreponemal antibody titers (eg, RPR, VDRL test) correlate with disease activity, generally increasing during primary or secondary syphilis and decreasing with spirochete inactivity, such as during latent syphilis or after adequate antibiotic treatment. They are useful barometers for monitoring therapy for both systemic and ocular disease. Results of treponemal tests (eg, FTA-ABS, syphilis IgG) become positive during the secondary stage of syphilis

Table 11-1 Types of Serologic Testing for Syphilis

Nontreponemal
Venereal Disease Research Laboratory (VDRL)
Rapid plasma reagin (RPR)
Treponemal
Treponema pallidum antibodies via enzyme immunoassays (EIAs) or chemiluminescence immunoassays (CIAs)
Microhemagglutination assay for *T pallidum* antibodies (MHA-TP)
Fluorescent treponemal antibody absorption (FTA-ABS) assay

and remain positive throughout the patient's life; as such, they are not useful in assessing therapeutic response.

As a result of passive transfer of IgG across the placenta, VDRL and FTA-ABS IgG test results are positive among infants born to mothers with syphilis. For this reason, serodiagnosis of congenital syphilis is made using the FTA-ABS IgM test, the results of which can indicate acute infection in an infant.

False-positive and false-negative results may occur with both types of tests. False-positive nontreponemal tests occur in various conditions, including the following:

- systemic lupus erythematosus and other autoimmune diseases
- pregnancy, vaccinations, advanced age, intravenous drug use
- infectious diseases such as leprosy, bacterial endocarditis, tuberculosis, infectious mononucleosis, HIV, atypical pneumonia, and malaria
- spirochetal infections (eg, rickettsial infections, Lyme disease, leptospirosis)
- other treponemal infections (yaws, pinta, and bejel)

False-positive treponemal test results are rare (1%–2%) and may be associated with similar conditions. False-negative nontreponemal testing may occur in primary or secondary syphilis when high antibody titers prevent formation of antibody/antigen complexes (the "prozone" effect), or in late-stage syphilis when spirochetes are inactive. Both treponemal and nontreponemal test results become positive approximately 2–4 weeks after infection, so false-negative tests may occur in asymptomatic patients with recent exposure. Both the false-positive and false-negative rates of serologic testing may be greater in HIV-infected patients.

Patients with syphilitic uveitis may require a lumbar puncture with examination of cerebrospinal fluid (CSF), especially if they have neurologic symptoms. A positive CSF-VDRL result and/or pleocytosis is diagnostic for neurosyphilis, as the CSF-VDRL can be nonreactive in some cases of active CNS involvement. In patients with neurosyphilis and abnormal CSF findings, spinal fluid examinations must be repeated every 6 months until the cell count and protein level return to normal and the VDRL is nonreactive.

Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for Syphilis: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2016; 315(21):2328–2337.

Other diagnostic techniques

Primary syphilis can be diagnosed by direct visualization of spirochetes with dark-field microscopy and by direct fluorescent antibody tests of lesion exudates or tissue. Polymerase chain reaction (PCR)-based DNA amplification techniques may be used on intraocular fluids, CSF fluids, or fluid taken from swabs of mucosal sites or ulcerative lesions.

Treatment

For all stages of syphilis, parenteral penicillin G is the preferred treatment. Regardless of immune status, patients with syphilitic uveitis should be treated with the regimen used for neurosyphilis: intravenous aqueous penicillin G for 10–14 days. Penicillin is the first choice for neurosyphilis, congenital infection, or infection in people who are pregnant or coinfected with HIV. Patients with penicillin allergy may require desensitization. For penicillin-allergic

patients who do not have neurosyphilis or HIV coinfection, alternatives include doxycycline or tetracycline. For penicillin-allergic patients with ocular syphilis, ceftriaxone and chloramphenicol have been reported to be effective alternatives.

In the first 24 hours of treatment, patients should be monitored for the development of the *Jarisch-Herxheimer reaction,* a hypersensitivity response of the host to treponemal antigens released in large numbers as spirochetes are killed. Patients can have constitutional symptoms such as fever, chills, hypotension, tachycardia, and malaise, and they may also experience concomitant worsening of intraocular inflammation that may require local and/or systemic corticosteroids. In most cases, supportive care and observation are sufficient.

Topical, periocular, and/or systemic corticosteroids, with concurrent antibiotic treatment, may be useful adjuncts for treating the intraocular inflammation associated with syphilitic uveitis. Use of systemic, periocular, or intravitreal corticosteroids in patients with undiagnosed syphilis can worsen the disease and may result in irreversible vision loss. When the diagnosis of ocular syphilis is significantly delayed, patients may develop chronic uveitis that requires ongoing anti-inflammatory treatment after the antibiotic course is completed.

Centers for Disease Control and Prevention. *Sexually Transmitted Infections Treatment Guidelines, 2021*. US Dept of Health and Human Services. Accessed September 15, 2022. https://www.cdc.gov/std/treatment-guidelines/

Queiroz RP, Smit DP, Peters RPH, Vasconcelos-Santos DV. Double trouble: challenges in the diagnosis and management of ocular syphilis in HIV-infected individuals. *Ocul Immunol Inflamm*. 2020;28(7):1040–1048.

Tuberculosis

Tuberculosis (TB) is a rare cause of ocular disease in the United States. The TB incidence rate in the United States has decreased from 52.6 cases per 100,000 persons in 1953 to 2.2 cases per 100,000 in 2020. Worldwide, however, TB remains an important systemic infectious disease, with more than 10.4 million new cases and 1.7 million deaths reported annually. Nearly one-third of the world's population is infected, and 95% of cases occur in resource-limited countries. In the United States, the incidence of uveitis attributable to TB at tertiary care clinics is less than 1%, whereas at referral centers in India, the incidence is up to 10%.

The most important risk factor for TB infection in the United States is country of birth, with 71.5% of infections occurring in persons born outside the United States. Additional risk factors include medical conditions such as diabetes and HIV infection and social and occupational factors such as homelessness, substance use, and employment or residence in a congregate setting (eg, a correctional facility or long-term care facility).

Mycobacterium tuberculosis, the etiologic agent of TB, is an acid-fast–staining obligate aerobe most commonly transmitted in aerosolized droplets. The organism has an affinity for highly oxygenated tissues, so tubercular lesions are commonly found in the apices of the lungs as well as in the choroid. While primary infection may occur due to recent exposure to *M tuberculosis,* the majority of cases (up to 90%) develop as a result of reactivation of latent infection in immunocompromised patients. Immunocompromised patients are also at risk for widespread hematogenous dissemination of *M tuberculosis,* known as *miliary TB*.

Testing for TB exposure is typically completed in patients who are starting systemic immunosuppressive medication, especially tumor necrosis factor (TNF) inhibitors.

In approximately 80% of infected patients, pulmonary TB develops. Among the 20% with extrapulmonary disease, 50% have a normal chest radiograph, and up to 20% have a negative purified protein derivative (PPD) skin test. Patients coinfected with HIV are more likely to have extrapulmonary disease, especially with deteriorating immune function. The classic presentation of symptomatic disease—fever, night sweats, and weight loss—can occur in both pulmonary and extrapulmonary infection.

Alli HD, Ally N, Mayet I, Dangor Z, Madhi SA. Global prevalence and clinical outcomes of tubercular uveitis: a systematic review and meta-analysis. *Surv Ophthalmol.* 2022;67(3): 770–792.

Centers for Disease Control and Prevention. *Reported Tuberculosis in the United States, 2021*. US Dept of Health and Human Services; 2021. Accessed August 27, 2023. https://www.cdc.gov/tb/statistics/reports/2021/default.htm

Ocular Involvement

Most patients with TB-associated ocular inflammatory disease have no active TB infection elsewhere in the body. The ocular manifestations may result from either active ocular infection or an immunologic reaction to extraocular organism. External ocular findings include scleritis (especially necrotizing), phlyctenulosis, interstitial keratitis, and corneal infiltrates. Tubercular uveitis is typically a chronic granulomatous disease that may affect the anterior or posterior segment or both. While granulomatous anterior uveitis can be an isolated finding, it is more likely to occur with posterior segment disease. Anterior segment manifestations may include mutton-fat keratic precipitates, iris nodules, posterior synechiae, and secondary glaucoma (Fig 11-7), although nongranulomatous uveitis may also occur. Patients may experience a waxing and waning course, with the development of macular edema (Fig 11-8). Neuroretinitis can also occur.

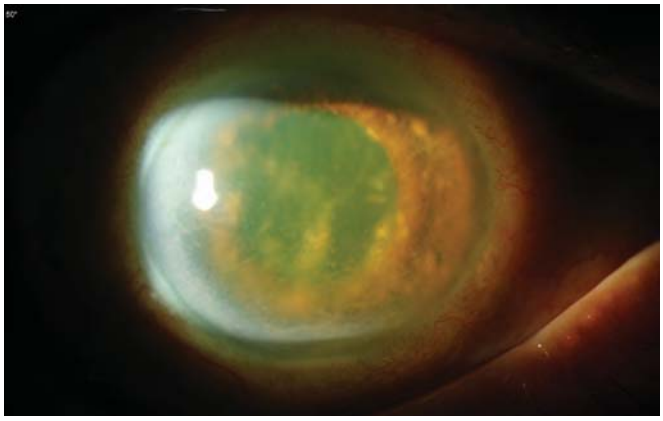

Figure 11-7 Ocular tuberculosis. Anterior segment photograph shows severe fibrinous inflammation and large iris nodules. Polymerase chain reaction testing of aqueous fluid was positive for *Mycobacterium tuberculosis*. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

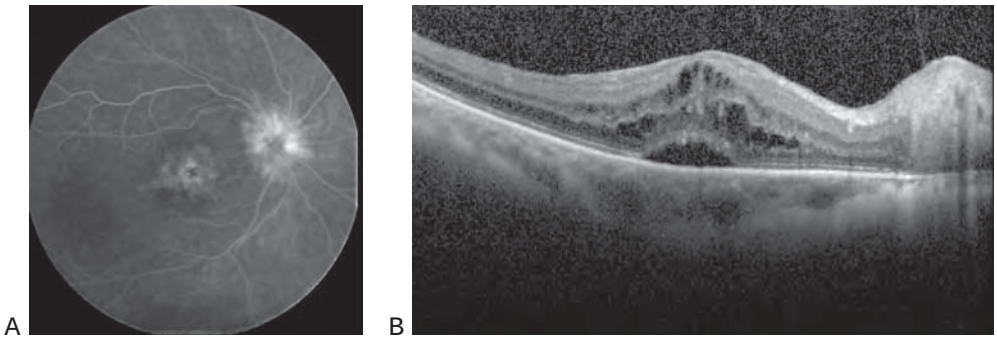

Figure 11-8 Chronic tuberculosis-associated uveitis. **A,** FA shows disc and macular leakage. **B,** SD-OCT confirms macular edema. *(Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.)*

CLINICAL PEARL

Possible ocular manifestations of TB include necrotizing scleritis, choroidal granuloma (tuberculoma), serpiginous-like choroiditis, and retinal vasculitis (often occlusive).

Choroidal involvement

The most common presentation is disseminated choroiditis that is characterized by multiple (from 5 to hundreds) deep, discrete, yellowish lesions (tubercles) between 0.5 mm and 3.0 mm in diameter (Fig 11-9). These lesions are located predominantly in the posterior pole and may be accompanied by granulomatous anterior uveitis, vitritis, disc edema, and nerve fiber layer hemorrhages. Alternatively, there can be a single, focal, large (4–14-mm), elevated choroidal mass (tuberculoma) that may be accompanied by neurosensory retinal detachment and macular star formation (Fig 11-10). Choroidal tubercles may be one of the earliest signs of disseminated disease and are more common in immunocompromised hosts. On FA, active choroidal lesions display early hypofluorescence and hyperfluorescence with late leakage, and cicatricial lesions show early blocked fluorescence with late staining. ICGA reveals early- and late-stage hypofluorescence corresponding to the choroidal lesions, which are frequently more numerous than those seen on clinical examination or FA. Other manifestations include multifocal choroiditis, frequently with a serpiginoid pattern termed *serpiginous-like choroiditis* (also called *multifocal serpiginoid choroiditis*) (Fig 11-11). In patients with HIV infection/AIDS, tubercular choroiditis may progress despite effective antituberculosis therapy.

Retinal involvement

Retinal involvement in TB is usually secondary to extension of the choroidal disease or an immunologic response to mycobacteria and should be differentiated from *Eales disease*, a peripheral retinal vasculitis that presents in otherwise healthy young men aged 20–40 years with recurrent, unilateral retinal and vitreous hemorrhage and subsequent involvement of the fellow eye. The disease may be associated with tuberculin hypersensitivity. Interestingly, a few studies employing PCR-based assays have detected *M tuberculosis* DNA in aqueous,

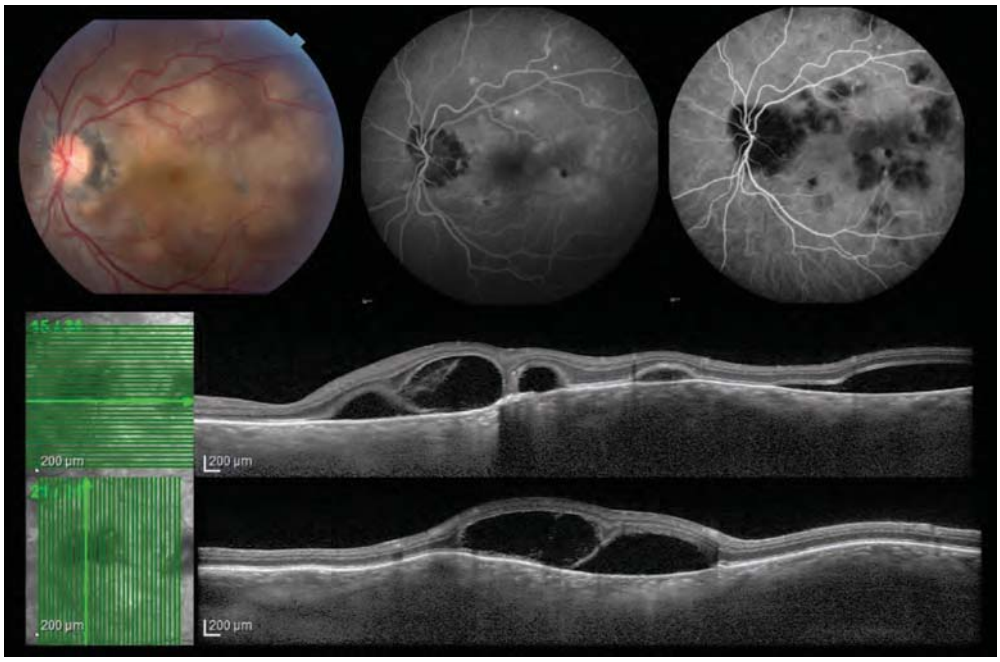

Figure 11-9 Tubercular multifocal choroiditis. Fundus photography *(top left)* shows multiple pockets of subretinal fluid overlying choroidal tubercles. FA *(top middle)* reveals multifocal leakage, and indocyanine green angiography *(top right)* delineates hypocyanescence, presumably corresponding to areas of choroidal inflammatory infiltration. SD-OCT *(bottom)* shows choroidal nodules (tubercles) with overlying bacillary detachments. *(Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.)*

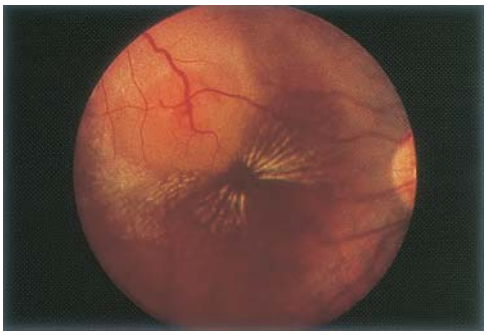

Figure 11-10 Ocular tuberculosis. Fundus photograph demonstrates a choroidal tubercle (tuberculoma) with a macular star formation).

vitreous, and epiretinal membranes from patients with Eales disease. Periphlebitis is commonly seen in patients with Eales disease and may be accompanied by venous occlusion, peripheral nonperfusion, neovascularization (Fig 11-12), and eventual development of tractional retinal detachment in some cases. See BCSC Section 12, *Retina and Vitreous,* for additional discussion of Eales disease.

Other posterior segment findings of TB include subretinal abscess, choroidal neovascularization, optic neuritis, and panophthalmitis.

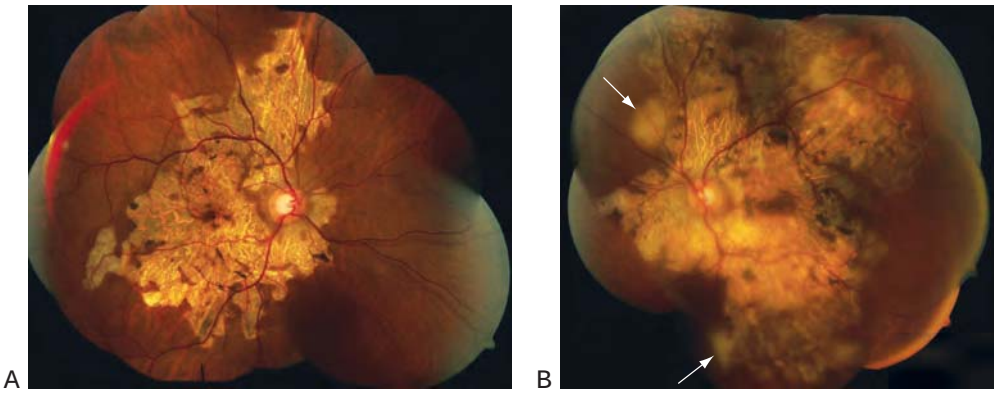

Figure 11-11 Ocular tuberculosis. Fundus photographs showing tubercular choroiditis masquerading as atypical serpiginous-like choroiditis. **A,** The right eye shows inactive disease. **B,** The left eye (from same patient as in part A) shows areas of new activity *(arrows)* as well as areas of scarring. *(Reproduced with permission from Leveque TK, Van Gelder RN. Uveitis. In: Stein HA, Stein RM, Freeman MI, Stein RL, eds.* The Ophthalmic Assistant: A Text for Allied and Associated Ophthalmic Personnel. *11th ed. Elsevier; 2022:484.)*

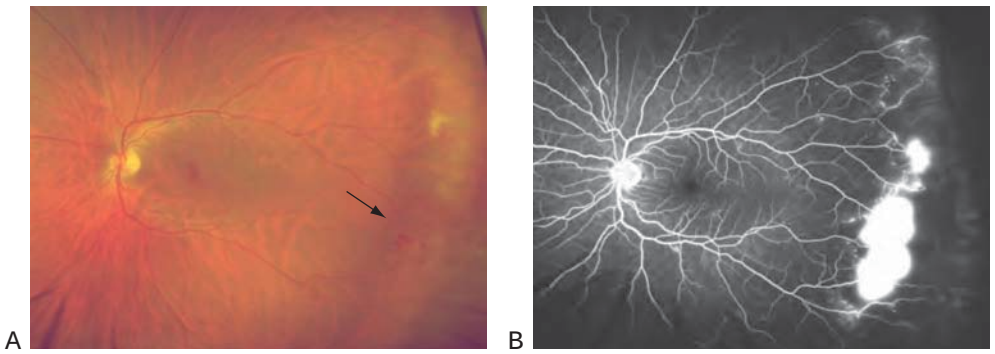

Figure 11-12 Eales disease. **A,** Wide-angle fundus photograph of Eales disease with retinal hemorrhage with neovascularization *(arrow)*. **B,** Angiographic image shows peripheral retinal nonperfusion and neovascularization (temporally), in addition to perivenular hyperfluorescence (periphlebitis). *(Courtesy of Emilio M. Dodds, MD.)*

Diagnosis

Definitive diagnosis of TB requires direct evidence of mycobacteria in bodily fluids or tissues. A history of recent exposure to TB or a positive TB test result warrants a concerted search for systemic infection using chest imaging, and/or microbiologic analysis of specimens from other body sites. However, failure to demonstrate systemic disease does not exclude the possibility of ocular involvement. In many cases of ocular TB, the diagnosis is presumptive and based on the presence of TB exposure risk factors, clinical findings of ocular disease consistent with TB (eg, choroidal granuloma, serpiginous-like choroiditis), and positive TB screening tests.

A positive result on the tuberculin skin test using PPD (purified protein derivative of *Mycobacterium bovis*) or the serum interferon-gamma release assay (IGRA) can indicate

previous exposure to TB, but it does not provide proof of active systemic or ocular infection. The IGRA blood test is useful when the patient has been immunized with the BCG vaccine; a positive IGRA result suggests exposure to TB, whereas an immune reaction to the PPD usually occurs in BCG-vaccinated patients and thus does not necessarily indicate TB infection. Antibodies against purified cord factor, the most antigenic and abundant cell wall component of tubercle bacilli, have been detected by enzyme-linked immunosorbent assay (ELISA) and may be useful for rapid serodiagnosis of pulmonary TB, in addition to providing supportive data for the diagnosis of ocular infection.

In cases of suspected ocular TB with no evidence of systemic infection, ocular fluid or tissue testing can be attempted. Nucleic acid amplification techniques, with either transcription-mediated amplification of 16S ribosomal RNA or PCR amplification of unique DNA sequences of *M tuberculosis,* can be used to detect intraocular TB. However, the yield from ocular fluids may be low because *M tuberculosis* has a thick cell wall and the organism is less likely to be present in aqueous or vitreous. In atypical or vision-threatening cases where it is important to rule out masquerade syndromes, chorioretinal biopsy in conjunction with PCR testing and routine histologic examination may be necessary.

Agarwal A, Agrawal R, Gunasekaran DV, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1 Report 3: Polymerase Chain Reaction in the Diagnosis and Management of Tubercular Uveitis: Global Trends. *Ocul Immunol Inflamm.* 2019;27(3):465–473.

Betzler BK, Gupta V, Agrawal R. Clinics of ocular tuberculosis: a review. *Clin Exp Ophthalmol.* 2021;49(2):146–160.

Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis.* 2017;64(2):111–115.

Testi I, Agrawal R, Mahajan S, et al. Tubercular uveitis: nuggets from Collaborative Ocular Tuberculosis Study (COTS)-1. *Ocul Immunol Inflamm.* 2020;28(sup1):8–16.

CLINICAL PEARL

In patients with uveitis, possible indications for TB testing include

- ocular findings suggestive of TB (ie, choroidal granuloma, serpiginous-like choroiditis, necrotizing scleritis)
- high pretest probability of TB because of risk factors for TB exposure and/or systemic symptoms that are concerning for TB infection
- screening before initiation of systemic immunosuppressive medication

Treatment

In brief, TB treatment entails an initial 2-month induction course of isoniazid, rifampin, pyrazinamide, and ethambutol (quadruple drug therapy), followed by 2-drug therapy for 4–7 months. More than 95% of immunocompetent patients may be successfully treated with a full course of therapy, provided they adhere to the regimen. Treatment protocols have been

standardized and are available from the CDC. Comanagement with an infectious diseases specialist and the local health department is usually recommended.

Because ocular TB can be a difficult diagnosis to definitively confirm, the treatment approach varies depending on the features of ocular disease and the likelihood of extraocular TB infection. Recently, the Collaborative Ocular Tuberculosis Study Consensus Group developed new guidelines for the management of tubercular uveitis that are based on multiple factors, such as the type of uveitis.

Indications to treat tubercular uveitis with quadruple drug therapy include (1) recent conversion to a positive TB test; (2) chest radiograph findings consistent with TB; (3) positive mycobacterial culture or *M tuberculosis* PCR. If a patient with suspected tubercular uveitis has a positive TB test and a normal chest radiograph, quadruple drug therapy may be indicated when the ocular inflammation is strongly suggestive of TB or the uveitis has been recalcitrant to systemic immunomodulatory therapy (IMT).

After quadruple drug therapy is started, tubercular uveitis may paradoxically worsen, requiring concurrent treatment with corticosteroids (topical and/or systemic) for the inflammatory component of the disease. Delayed diagnosis may lead to chronic tubercular uveitis; after at least one month of quadruple drug therapy, cautious initiation of systemic immunosuppressive medication may be considered with the agreement of the infectious diseases specialist.

As mentioned previously, because there is a risk of reactivation of latent infection, all patients should be screened for TB exposure before starting systemic IMT, especially TNF inhibitors. Patients with latent TB may be treated for 6–12 months with isoniazid with or without rifapentine or rifampin.

Agrawal R, Gunasekeran DV, Grant R, et al; Collaborative Ocular Tuberculosis Study (COTS)–1 Study Group. Clinical features and outcomes of patients with tubercular uveitis treated with antitubercular therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1. *JAMA Ophthalmol.* 2017;135(12):1318–1327.

Agrawal R, Testi I, Bodaghi B, et al; Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis—Report 2: Guidelines for Initiating Antitubercular Therapy in Anterior Uveitis, Intermediate Uveitis, Panuveitis, and Retinal Vasculitis. *Ophthalmology.* 2021;128(2):277–287.

Agrawal R, Testi I, Mahajan S, et al; Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis—Report 1: Guidelines for Initiating Antitubercular Therapy in Tubercular Choroiditis. *Ophthalmology.* 2021;128(2):266–276.

Lyme Disease

Lyme disease (LD) is the most common tick-borne illness in the United States, where it is caused by the spirochete *Borrelia burgdorferi*. Outside the United States, LD is caused by different *Borrelia* species, including *Borrelia afzelii* and *Borrelia garinii.* Animal reservoirs include deer, horses, cows, rodents, birds, cats, and dogs. The spirochete is transmitted to humans through the bite of an infected tick, *Ixodes scapularis* in the northeast, mid-Atlantic,

and midwestern United States and *Ixodes pacificus* in the western United States. The disease affects men (53% of cases) slightly more often than women, and it has a bimodal age distribution, with peaks in children aged 5–14 years and in adults aged 50–59 years. There is a seasonal variation, with most cases occurring between May and August. Prevention strategies include avoiding tick-infested habitats, using tick repellents, wearing protective outer garments, removing ticks promptly, and reducing tick populations.

Clinical Features

The 3 stages of LD have protean systemic manifestations. Intraocular inflammation is very rare. See BCSC Section 1, *Update on General Medicine,* for more information about LD.

Stage 1

The most characteristic feature of stage 1, or *localized* disease, is a macular rash known as *erythema chronicum migrans* at the site of the tick bite (Fig 11-13). It appears within 2–28 days of the bite in at least 70% of patients, often appearing as a "bull's-eye" lesion with central clearing. Constitutional symptoms appear at this stage and include fever, malaise, fatigue, myalgias, and arthralgias.

Stage 2

Stage 2, or *early disseminated* disease, occurs days to weeks after exposure. Spirochetes spread hematogenously to the skin, CNS, joints, heart, and eyes. A secondary erythema chronicum migrans rash may appear at sites remote from the tick bite. If LD is left untreated, up to 80% of patients with erythema chronicum migrans develop joint manifestations, most commonly monoarthritis or oligoarthritis involving the large joints, typically the knee.

Neurologic involvement, which occurs in up to 15% of untreated patients with LD, can develop in stage 2 or 3. Lyme neuroborreliosis may include meningitis, encephalitis, painful radiculitis, or unilateral or bilateral Bell palsy. In endemic areas, as many as 25% of new-onset cranial nerve VII palsies may be attributed to *B burgdorferi* infection.

Stage 3

Stage 3, or *late disseminated* disease, occurs more than 5 months after the initial infection. The most frequent systemic manifestation is episodic arthritis that may become chronic and is associated with human leukocyte antigen (HLA)-DR4 and -DR2 haplotypes in North

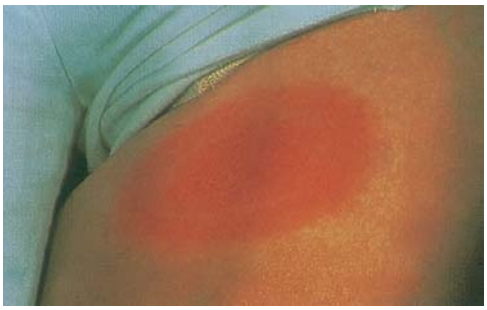

Figure 11-13 Lyme disease. External photograph shows a single dense erythematous lesion consistent with erythema chronicum migrans in a patient with Lyme disease. *(Courtesy of Alan B. MacDonald, MD.)*

America. Chronic systemic findings include acrodermatitis chronica atrophicans, neuropsychiatric disease, radiculopathy, chronic fatigue, peripheral neuropathy, and memory loss.

Steere AC, Strle F, Wormser GP, et al. Lyme borreliosis. *Nat Rev Dis Primers.* 2016;2:16090. doi:10.1038/nrdp.2016.90

Ocular Involvement

The spectrum of ocular findings in patients with LD varies with disease stage.

In early stage 1 disease, the most common ocular finding, occurring in approximately 11% of patients, is a follicular conjunctivitis. Episcleritis is a less frequent manifestation.

Intraocular inflammation is a rare manifestation of LD. It has been reported in stage 2 and, rarely, in stage 3 disease. All forms of uveitis have been described, with intermediate uveitis being the most common. Vitritis may be severe and accompanied by a granulomatous anterior chamber reaction. Other findings include choroiditis, retinal vasculitis, and exudative retinal detachment. A type of peripheral multifocal choroiditis has been described in patients with LD and is characterized by multiple small, round, punched-out lesions associated with vitritis, similar to those present in sarcoidosis. Choroidal involvement may lead to pigment epithelial clumping resembling the inflammatory changes that occur with syphilis or rubella. Retinal vasculitis, found in association with peripheral multifocal choroiditis or vasculitic branch retinal vein occlusion, may be more common than previously known.

Neuro-ophthalmic manifestations of LD occur more frequently than uveitis. In stage 2, multiple cranial neuropathies can occur, unilaterally or bilaterally, either sequentially or simultaneously. Optic nerve findings include papillitis (most common), neuroretinitis, optic neuritis, and papilledema associated with meningitis. Horner syndrome has also been reported.

The most common ocular manifestation of stage 3 disease is presumed immune-mediated keratitis. In rare cases, episcleritis may occur. Both may present months to years after the onset of infection. Typically, infiltrates are bilateral, patchy, focal, and stromal. Subepithelial infiltrates with indistinct borders, peripheral keratitis with stromal edema, and corneal neovascularization can also occur.

Bernard A, Seve P, Abukhashabh A, et al. Lyme-associated uveitis: clinical spectrum and review of literature. *Eur J Ophthalmol.* 2020;30(5):874–885.

Sathiamoorthi S, Smith WM. The eye and tick-borne disease in the United States. *Curr Opin Ophthalmol.* 2016;27(6):530–537.

Diagnosis

It should be emphasized that intraocular inflammation is not a common manifestation of LD. In a patient with no risk factors for tick bite and no signs or symptoms of systemic inflammatory disease, it is very unlikely that new-onset uveitis is related to LD. Therefore, serologic screening for LD does not need to be part of a standard workup for new-onset uveitis.

The diagnosis of early LD can be made on the basis of the history and clinical presentation. For example, if a patient in a Lyme-endemic area presents with a bull's-eye rash after a tick bite, a primary care provider may opt to treat with a course of antibiotics for presumed LD. Otherwise, for the diagnosis of active LD or previous infection, the CDC recommends

serum ELISA testing for Lyme IgM and IgG, followed by confirmatory Western immunoblot testing. False-positive results can occur in patients with syphilis or other infections, as well as in various rheumatologic diseases. Similar to the approach used for patients with syphilitic uveitis, investigations for CNS disease may be warranted for patients with uveitis and LD.

Caplash S, Gangaputra S, Kesav N, et al. Usefulness of routine Lyme screening in patients with uveitis. *Ophthalmology.* 2019;126(12):1726–1728.

Rifkin LM, Vadboncoeur J, Minkus CC, et al. The utility of Lyme testing in the workup of ocular inflammation. *Ocul Immunol Inflamm.* 2021;29(1):149–153.

Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease—United States, 2008–2015. *MMWR Surveill Summ.* 2017;66(22):1–12.

Treatment

Treatment for LD is based on the stage of infection. Oral antibiotic regimens include amoxicillin, 500 mg 3 times/day; doxycycline, 100 mg 2 times/day; or cefuroxime axetil, 500 mg 2 times/day. For patients with ocular involvement, the route of administration and duration of antibiotic treatment have not been established. Those with severe posterior segment involvement may be treated with intravenous (IV) antibiotics according to dosing regimens for neurologic LD (ie, ceftriaxone 2 g IV daily, cefotaxime 2 g IV every 8 hours, or penicillin G 18–24 million units/day IV divided every 4 hours). As with syphilis, the Jarisch-Herxheimer reaction may complicate antibiotic therapy.

After appropriate antibiotic therapy is initiated, anterior segment inflammation may be treated with topical corticosteroids and mydriatics. The use of systemic corticosteroids has been described as part of the management of LD; however, the routine use of corticosteroids is controversial, as it has been associated with an increase in antibiotic treatment failures.

Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease. *Arthritis Care Res (Hoboken).* 2021;73(1):1–9.

Leptospirosis

Leptospirosis is a zoonotic infection with a worldwide distribution. It occurs most frequently in tropical and subtropical regions and is caused by the gram-negative spirochete *Leptospira interrogans.* The natural reservoirs for *Leptospira* organisms include livestock, horses, dogs, and rodents, which excrete the organism in their urine. Humans contract the disease upon exposure to contaminated soil or water; thus, groups at risk include agricultural workers, sewer workers, veterinarians, fishery and slaughterhouse workers, and military personnel, as well as swimmers, triathletes, and whitewater rafters. The disease is not known to spread from person to person, but maternal–fetal transmission might occur infrequently. Leptospirosis is very rare in the United States, with 100–150 cases identified annually, half of them in Puerto Rico. Globally, 1 million people are estimated to be infected each year, with almost 60,000 deaths. Since 2013, leptospirosis has been reinstated as a nationally notifiable disease in the United States.

Leptospirosis is frequently a biphasic disease. The initial, or *leptospiremic,* phase follows an incubation period of 2–4 weeks and is heralded by the abrupt onset of fever, chills, headache, myalgias, vomiting, and diarrhea. Approximately 10% of infected individuals will develop severe septicemic leptospirosis or *Weil disease,* which is characterized by renal and hepatocellular dysfunction and is fatal in 30% of cases. Leptospires may be isolated from the blood and CSF but are cleared rapidly as the disease progresses to the second, or *immune,* phase, which is characterized by meningitis, leptospiruria, cranial nerve palsies, myelitis, and uveitis. The organism may persist for longer periods in immunologically privileged sites, such as the brain and the eye.

Centers for Disease Control and Prevention. *Leptospirosis: Healthcare Workers.* US Dept of Health and Human Services; 2018. Accessed November 28, 2022. http://www.cdc.gov/leptospirosis/health_care_workers/index.html

Ocular Involvement

Ocular involvement can occur in both the leptospiremic and immune phases, but frequently there is a prolonged interval between systemic and ocular disease. The earliest and most common sign of ocular leptospirosis is circumcorneal conjunctival hyperemia. The development of intraocular inflammation (in 10%–44% of patients) can manifest as mild anterior uveitis, neuroretinitis, or panuveitis with retinal vasculitis and is the more serious, potentially vision-threatening complication.

Sivakumar RR. Ocular leptospirosis: lack of awareness among ophthalmologists and challenges in diagnosis. *Curr Opin Ophthalmol.* 2022;33(6):532–542.

Diagnosis

The differential diagnosis of leptospiral uveitis includes HLA-B27–associated uveitis, idiopathic pars planitis, Behçet disease, Eales disease, sarcoidosis-associated uveitis, and tubercular and syphilitic uveitis. Appropriate history and laboratory evaluation help distinguish these entities from leptospiral uveitis. A definitive diagnosis requires isolation of the organism from bodily fluids. A presumptive diagnosis is made on the basis of serologic assays. Rapid serologic assays such as ELISA and complement-fixation tests for the detection of IgM antibodies against leptospiral antigens are highly sensitive and specific; PCR-based assays are under evaluation. Leptospirosis may cause a false-positive result on the RPR or FTA-ABS test.

Treatment

For mild or moderate cases, penicillin G (1.5 million units IV every 6 hours) or oral doxycycline (100 mg twice daily for 1 week) may be used. It is not known whether systemic antibiotic treatment can prevent long-term complications such as uveitis. However, systemic antibiotic treatment should be considered for ocular disease that occurs even months after onset of the acute systemic disease. In addition, topical, periocular, or systemic corticosteroids, together with mydriatic and cycloplegic drugs, are routinely used to treat intraocular inflammation and complications. The visual prognosis for patients with leptospiral uveitis is quite favorable despite severe panuveitis.

Nocardiosis

Nocardia asteroides is a gram-positive rod with partially acid-fast beaded branching filaments—a bacterium that acts like a fungus. The organism is commonly found in soil, and initial infection occurs by ingestion or inhalation, causing an insidious inflammation. Immunocompromised individuals are more likely to be infected than immunocompetent persons. *N asteroides* causes a potentially lethal disease characterized by pneumonia and disseminated abscesses. Ocular involvement is rare, but it may be the presenting problem.

Garg P. Fungal, mycobacterial, and *Nocardia* infections and the eye: an update. *Eye (Lond).* 2012;26(2):245–251.

Ocular Involvement

Ocular involvement occurs by hematogenous spread of the bacteria, and essentially any ocular structure can be affected, including periorbital tissue and the adnexa. Symptoms vary from the mild pain and redness of anterior uveitis to severe pain and decreased vision from panophthalmitis. Findings may include keratitis; necrotizing scleritis; or an isolated, unilateral choroidal or subretinal mass or abscess (Fig 11-14) with minimal vitritis. Panuveitis may also develop, with anterior chamber cell and flare, vitritis, and multiple choroidal abscesses with overlying retinal detachments mimicking fungal endophthalmitis.

Diagnosis

Diagnosis can be established with a culture of the organism taken from tissue or fluid, by vitreous aspiration for Gram stain and culture, or occasionally by enucleation and microscopic identification of *N asteroides*. Where available, molecular techniques such as panbacterial 16S ribosomal RNA PCR or PCR for *Nocardia* species may be used.

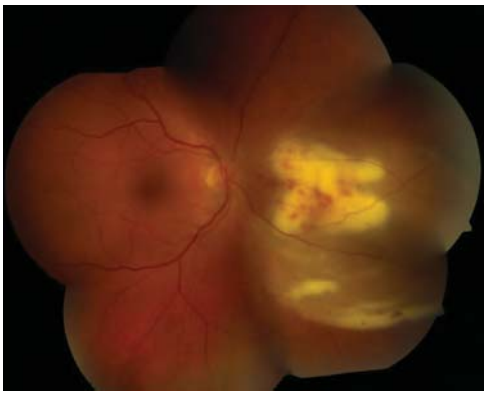

Figure 11-14 Ocular nocardiosis. Fundus photograph reveals a subretinal abscess in the nasal retina. *(Courtesy of Gaurav K. Shah, MD.)*

Treatment

Treatment of *N asteroides* infection with systemic sulfonamide (trimethoprim-sulfamethoxazole) may be required for protracted periods. Combination therapy with additional antibiotics may be necessary.

Bartonellosis

Bartonella henselae is a small, fastidious gram-negative rod that was initially isolated from the tissue of patients with bacillary angiomatosis of AIDS. It is known to be the principal etiologic agent of cat-scratch disease (CSD), a feline-associated zoonotic disease. CSD is found worldwide, with an estimated annual incidence rate in the United States of 9.3 cases per 100,000 persons. The highest age-specific incidence is among children younger than 10 years. Cats are the primary mammalian reservoir of *B henselae* and other species that can cause CSD, such as *Bartonella quintana.* The cat flea is an important vector for the transmission of these organisms among cats. CSD is transmitted to humans by the scratches, licks, and bites of domestic cats, particularly kittens. The disease follows a seasonal pattern, occurring predominantly in the fall and winter, and is most prevalent in the southern states, California, and Hawaii.

Systemic manifestations of CSD include a mild to moderate flulike illness associated with regional adenopathy that usually precedes the ocular manifestations of the disease. An erythematous papule, vesicle, or pustule usually forms at the primary site of cutaneous injury 3–10 days after primary inoculation and 1–2 weeks before the onset of lymphadenopathy and constitutional symptoms. Less commonly, more severe and disseminated disease may develop that is associated with encephalopathy, aseptic meningitis, osteomyelitis, hepatosplenic disease, pneumonia, and pleural and pericardial effusions.

Biancardi AL, Curi AL. Cat-scratch disease. *Ocul Immunol Inflamm.* 2014;22(2):148–154.

Ocular Involvement

Ocular involvement occurs in 5%–10% of patients with CSD and includes Parinaud oculoglandular syndrome (unilateral granulomatous conjunctivitis and regional lymphadenopathy) in approximately 5% of patients. The differential diagnosis of Parinaud oculoglandular syndrome includes tularemia, TB, syphilis, sporotrichosis, and acute *Chlamydia trachomatis* infection. See BCSC Section 8, *External Disease and Cornea,* for further discussion.

Ocular bartonellosis has a wide array of posterior segment and neuro-ophthalmic findings. Although the most common finding in *B henselae* infection is a small focal area of retinitis, the best-known posterior segment manifestation is neuroretinitis, which occurs in 1%–2% of patients with CSD and follows the onset of constitutional symptoms by 2–3 weeks. It is characterized by abrupt vision loss, unilateral optic disc edema, and macular star formation with or without focal or multifocal retinitis. Visual acuity ranges from 20/25 to 20/200 or worse. Although the presentation is most often unilateral, bilateral cases of neuroretinitis have been reported and are frequently asymmetric. Optic disc edema, associated with

peripapillary serous retinal detachment, has been observed 2–4 weeks before the appearance of the macular star and may be a sign of systemic *B henselae* infection. The development of the macular star is variable (Fig 11-15) and may be partial or incomplete, usually resolving in approximately 8–12 weeks. Table 11-2 lists other entities that may cause neuroretinitis.

Patients with *Bartonella*-associated neuroretinitis may exhibit some degree of anterior chamber inflammation and vitritis. Discrete, focal, or multifocal retinal and/or choroidal

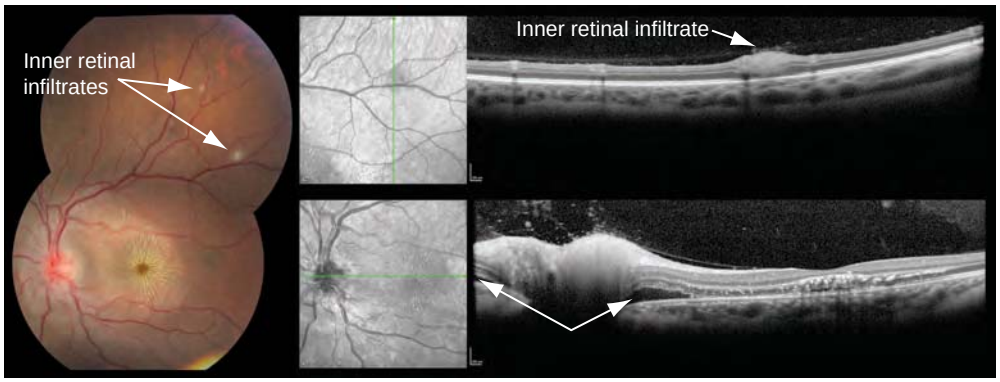

Figure 11-15 Ocular bartonellosis. *Left,* Color fundus photograph of the left eye of a patient with cat-scratch disease shows neuroretinitis with optic disc involvement associated with a macular star. Punctate retinal infiltrates (retinitis) are also visible superiorly *(arrows). Upper right,* SD-OCT scan delineates the inner retinal infiltrate *(arrow). Lower right,* The scan reveals subretinal fluid (peripapillary serous retinal detachments, *arrows*), intraretinal exudates, vitreous inflammatory infiltration, and optic disc and macular edema. *(Courtesy of Daniel V. Vasconcelos-Santos, MD, PhD.)*

Table 11-2 Differential Diagnosis of Neuroretinitis

Infectious conditions	
Bartonellosis *(Bartonella henselae)*	Mumps
Diffuse unilateral subacute neuroretinitis *(Ancylostoma caninum, Baylisascaris procyonis)*	Rocky Mountain spotted fever
	Salmonella
	Syphilis
	Toxocariasis
Ehrlichiosis	Toxoplasmosis
Herpes simplex	Tuberculosis
Leptospirosis	Varicella
Lyme disease	
Noninfectious conditions	
Acute systemic hypertension	Idiopathic intracranial hypertension
Anterior ischemic optic neuropathy	Leukemic infiltration of the optic nerve
Diabetes	Sarcoidosis
Idiopathic condition	
Recurrent idiopathic neuroretinitis	

lesions measuring 50–300 μm are common posterior segment findings. Both arterial and venous occlusive disease, as well as localized neurosensory macular detachments, have been described in association with focal retinitis. Other posterior segment ocular complications include epiretinal membranes, inflammatory mass of the optic nerve head, peripapillary angiomatosis, intermediate uveitis, retinal white dot syndromes, orbital abscess, isolated optic disc edema, and panuveitis. Immunosuppressed individuals may display a retinal vasoproliferative response, leading to single or multiple angiomatoid lesions involving retina and/or choroid.

Amer R, Tugal-Tutkun I. Ophthalmic manifestations of bartonella infection. *Curr Opin Ophthalmol.* 2017;28(6):607–612.

Chi SL, Stinnett S, Eggenberger E, et al. Clinical characteristics in 53 patients with cat scratch optic neuropathy. *Ophthalmology.* 2012;119(1):183–187.

Johnson A. Ocular complications of cat scratch disease. *Br J Ophthalmol.* 2020;104(12): 1640–1646.

Diagnosis

A diagnosis of CSD is made on the basis of characteristic clinical features together with confirmatory serologic testing. Serum anti–*B henselae* antibodies can be detected with indirect fluorescent antibody assay, enzyme immunoassays, or Western blot analysis; all methodologies have good sensitivity and specificity. A single positive indirect fluorescent antibody or enzyme immunoassay titer for IgG or IgM is sufficient to confirm the diagnosis of CSD. Other diagnostic approaches include bacterial cultures that may require several weeks for colonies to become apparent; skin testing, which has a sensitivity of up to 100% and a specificity of up to 98%; and PCR-based techniques that target the bacterial 16S ribosomal RNA gene or *B henselae* DNA.

Suhler ED, Lauer AK, Rosenbaum JT. Prevalence of serologic evidence of cat scratch disease in patients with neuroretinitis. *Ophthalmology.* 2000;107(5):871–876.

Treatment

Definitive treatment guidelines have not emerged for CSD because in many cases it is a self-limiting illness with an overall excellent systemic prognosis. Visual outcomes vary, depending on the location and severity of intraocular inflammation. A variety of antibiotics, including doxycycline, ciprofloxacin, erythromycin, rifampin, trimethoprim-sulfamethoxazole, and gentamicin, have been used in the treatment of more severe systemic or ocular manifestations, even though their efficacy has not been demonstrated conclusively. A typical regimen for immunocompetent patients older than 8 years consists of doxycycline, 100 mg orally twice daily for 4–6 weeks. For more severe infections, doxycycline may be given intravenously or used in combination with rifampin, 300 mg orally twice daily; in immunocompromised individuals, this treatment is extended for 4 months. Children with CSD may be treated with azithromycin. The effectiveness of oral corticosteroids on the course of systemic and ocular disease is unknown, even though these agents are frequently used in cases in which the optic nerve/macula is threatened.

Whipple Disease

Whipple disease is a rare multisystem disease caused by the *Tropheryma whipplei* bacterium. It is most common in middle-aged White men. Migratory arthritis occurs in 80% of cases, and gastrointestinal symptoms, including diarrhea, steatorrhea, and malabsorption, occur in 75%. Intestinal loss of protein results in pitting edema and weight loss. Cardiomyopathy and valvular disease can also occur. CNS involvement occurs in 10% of cases and causes seizures, dementia, and coma. Neuro-ophthalmic signs can include cranial nerve palsies, nystagmus, and ophthalmoplegia. Some patients develop a progressive supranuclear palsy–like condition. See also BCSC Section 5, *Neuro-Ophthalmology,* for discussion of the neuro-ophthalmic manifestations of Whipple disease.

Ocular Involvement

Intraocular involvement is rare, occurring in less than 5% of cases. Patients can present with bilateral panuveitis and retinal vasculitis, as well as with multifocal chorioretinitis (Fig 11-16). Both anterior uveitis and moderate vitritis are present. Diffuse chorioretinal inflammation and diffuse retinal vasculitis in the perifoveal and midperipheral regions may occur. Retinal vascular occlusions and retinal hemorrhages may result from the vasculitis. Optic disc edema and, later, optic atrophy may occur. Unusual granular, crystalline deposits on the iris, capsular bag, and intraocular lens have also been reported.

Touitou V, Fenollar F, Cassoux N, et al. Ocular Whipple's disease: therapeutic strategy and long-term follow-up. *Ophthalmology.* 2012;119(7):1465–1469.

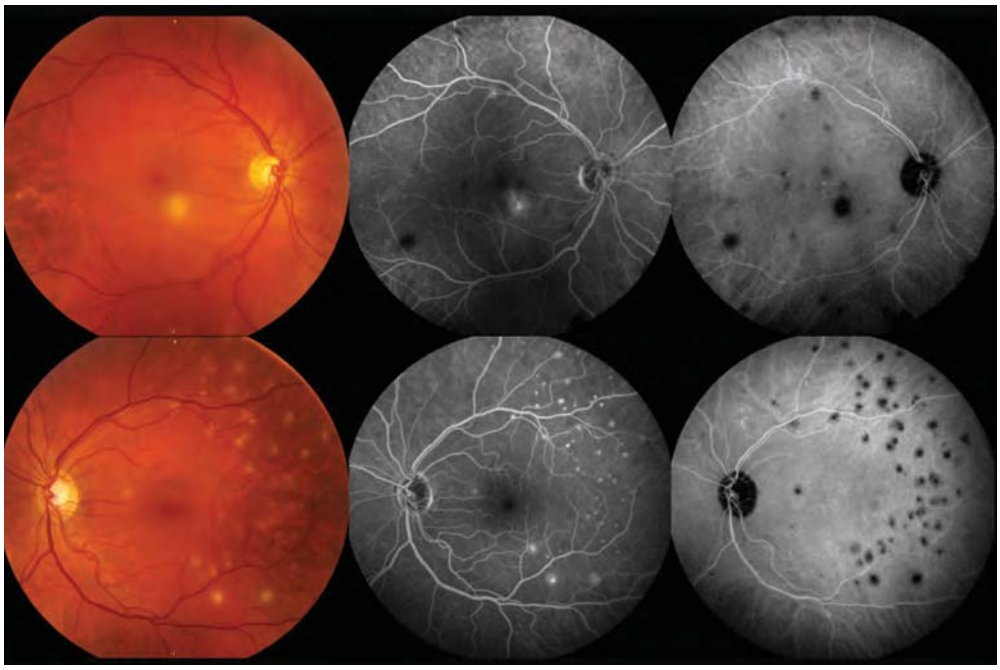

Figure 11-16 Whipple disease. Fundus photography *(left),* FA *(middle),* and indocyanine green angiography *(right)* demonstrate bilateral multifocal chorioretinitis. *(Courtesy of Wendy M. Smith, MD.)*

Diagnosis

The gold standard for diagnosis of Whipple disease is a duodenal biopsy that demonstrates a periodic acid–Schiff-positive bacillus in macrophages within intestinal villi. A PCR analysis of peripheral blood and vitreous may show *T whipplei* DNA and confirm the diagnosis. Culturing of *T whipplei* is difficult but possible. The differential diagnosis of uveitis associated with Whipple disease includes diseases that can cause retinal vasculitis with multisystem involvement, including sarcoidosis, systemic lupus erythematosus, polyarteritis nodosa, and Behçet disease. Vitreoretinal lymphoma should also be considered in older adults with substantial vitreal infiltration.

Boumaza A, Ben Azzouz E, Arrindell J, Lepidi H, Mezouar S, Desnues B. Whipple's disease and *Tropheryma whipplei* infections: from bench to bedside. *Lancet Infect Dis.* 2022;22(10):e280–e291. doi:10.1016/S1473-3099(22)00128-1

Treatment

Comanagement with an infectious diseases specialist is warranted. The preferred treatment is systemic trimethoprim-sulfamethoxazole. Patients allergic to sulfonamides may be treated with ceftriaxone, tetracycline, or chloramphenicol. Treatment duration may vary from 1 to 3 months, but relapses occur in 30% of cases, necessitating prolonged (up to 1 year) treatment. Retinal vasculitis can resolve with treatment, but neurologic deficits become permanent. Untreated, Whipple disease can be fatal.