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■ ■FURTHER READING Barberis C et al: Antimicrobial susceptibility of clinical isolates of Actinomyces and related genera reveals an unusual clindamycin resistance among Actinomyces urogenitalis strains. J Glob Antimicrob Resist 8:115, 2017. Bonnefond S et al: Clinical features of actinomycosis: A retrospective, multicenter study of 28 cases of miscellaneous presentations. Medi cine 95:e3923, 2016. Brody A et al: Targeted histological evaluation shows high incidence of Actinomyces infection in medication-related osteonecrosis of the jaws. Sci Rep 12:3406, 2022. Fong P et al: Identification and diversity of Actinomyces species in a clinical microbiology laboratory in the MALDI-TOF MS era. Anaer obe 54:151, 2018. Heo SH et al: Imaging of actinomycosis in various organs: A compre hensive review. Radiographics 34:19, 2014. Jeffery-Smith A et al: Is the presence of Actinomyces spp. in blood culture always significant? J Clin Microbiol 54:1137, 2016. Karanfilian KM et al: Cervicofacial actinomycosis. Int J Dermatol 59:1185, 2020. Kononen E, Wade WG: Actinomyces and related organisms in human infections. Clin Microbiol Rev 28:419, 2015. Lo Muzio L et al: The contribution of histopathological examination to the diagnosis of cervico-facial actinomycosis: A retrospective analysis of 68 cases. Eur J Clin Microbiol Infect Dis 33:1915, 2014. Lynch T et al: Species-level identification of Actinomyces isolates caus ing invasive infections: Multiyear comparison of Vitek MS (matrixassisted laser desorption ionization-time of flight mass spectrometry) to partial sequencing of the 16S rRNA gene. J Clin Microbiol 54:712, 2016. Qiu L et al: Pulmonary actinomycosis imitating lung cancer on (18) F-FDG PET/CT: A case report and literature review. Korean J Radiol 16:1262, 2015. Yang WT, Grant M: Actinomyces neuii: A case report of a rare cause of acute infective endocarditis and literature review. BMC Infect Dis 19:511, 2019. Thomas A. Russo, Seth R. Glassman

Whipple Disease Whipple disease (WD), described by George Whipple in 1907, is a chronic infection caused by Tropheryma whipplei. Most commonly, years pass from the onset of symptoms to the recognition of the dis ease because of its rarity, its various manifestations mimicking other conditions, and the need to perform nonroutine diagnostic tests. The long-held belief that WD is an infection was supported by observations on its responsiveness to antimicrobial therapy in the 1950s and the identification of bacilli via electron microscopy in small-bowel biopsy specimens in the 1960s. This hypothesis was finally confirmed by amplification and sequencing of a partial 16S rRNA polymerase chain reaction (PCR)–generated amplicon from duodenal tissue in 1991. The subsequent successful cultivation of T. whipplei enabled whole genome sequencing and the development of additional diagnostic tests. The development of PCR-based diagnostics has broadened our understanding of both the epidemiology of and the clinical syndromes attributable to T. whipplei. Exposure to T. whipplei, which appears to be much more common than has been appreciated, can be followed by asymptomatic carriage, acute disease, or chronic infection. Chronic infection—WD—is a rare development after exposure. “Classic” WD is manifested by some

combination of arthralgias/arthritis, weight loss, chronic diarrhea, abdominal pain, and fever. Variable involvement at

other sites also occurs; neurologic and cardiac disease are most com mon. Acute infection and chronic organ disease in the absence of intes tinal involvement (see “Isolated Infection,” below) are described with increasing frequency. Since untreated WD is often fatal and delayed diagnosis may lead to irreparable organ damage (e.g., in the central nervous system [CNS]), knowledge of the clinical scenarios in which WD should be considered and of an appropriate diagnostic strategy is mandatory.

■ ■ETIOLOGIC AGENT T. whipplei is a weakly staining gram-positive bacillus. Genomic sequence data have revealed that the organism has a small (<1-megabase) chromosome, with many biosynthetic pathways absent or incomplete. This finding is consistent with a host-dependent intracellular pathogen or a pathogen that requires a nutritionally rich extracellular environment. It is one of the slowest growing human pathogens, with a doubling time of 18 days. A genotyping scheme based on a variable region has disclosed >100 genotypes to date. All genotypes appear to be capable of causing similar clinical syndromes. ■ ■EPIDEMIOLOGY WD is rare but has been increasingly recognized since the advent of PCR-based diagnostic tools. Prevalence had been previously esti mated at 1−3 cases per 1 million population, although a recent U.S. epidemiologic survey places the number closer to 10 cases per million. Seroprevalence studies indicate that ~50% of Western Europeans and ~75% of Africans from rural Senegal have been exposed to T. whipplei. Higher prevalence may be attributable to differences in sanitation. Humans are the only known host. In most studies, males more com monly develop WD; WD is more common in Caucasians and increases with age. To date, no clear animal or environmental reservoir has been demonstrated. However, the organism has been identified by PCR in sewage water and human feces. Workers with direct exposure to sewage are more likely to be asymptomatically colonized than controls, a pat tern suggesting fecal–oral spread. Fecal PCR detection rates of 38% among family members of carriers or patients with infection support oral–oral or fecal–oral spread, although a common environmental exposure cannot be excluded. Further, the development of acute T. whipplei pneumonia in children raises the possibility of droplet or airborne transmission. CHAPTER 181 Whipple Disease ■ ■PATHOGENESIS AND PATHOLOGY Rates of asymptomatic carriage of T. whipplei are far higher than rates of chronic infection (<0.01% of those exposed). Both decreased host pathogen-specific inflammatory response and pathogen-driven modulation of host inflammatory response likely play a role in estab lishing chronic infection. The human leukocyte antigen (HLA) alleles DRB1*)13 and DQB1*()06, which stimulate humoral rather than cellmediated immune responses, are associated with an increased risk of infection. However, only a minority of infected patients possess these haplotypes, suggesting a role for other host factors. IRF4, a transcrip tion factor involved with the immune response, could be such a factor as evidenced by four related family members with WD who possessed IFR4 haploinsufficiency due to a loss-of-function mutation; the distri bution of WD in this extended family was consistent with an autosomal dominant trait with incomplete penetrance. Flow cytometry performed in WD patients demonstrates B-cell sub set abnormalities when compared to matched controls. Chronic infec tion is associated with an impaired TH1 response, enhanced production of anti-inflammatory cytokines, increased activity of regulatory T cells, M2 polarization of macrophages with diminished antimicrobial activity and impaired phagosome–lysosome fusion and ensuing apoptosis, and blunted development of T. whipplei–specific T cells. Therapies that blunt cell-mediated host

immune responses (e.g. systemic glucocorticoids or anti–tumor necrosis factor α [TNF-α] agents) may accelerate progression of chronic disease. Impaired cell-mediated immunity may play a role in establishing chronic carriage of T. whipplei, as is evidenced by higher rates of detection in the secretions of HIV-infected persons. T. whipplei has a tropism for myeloid cells, which it invades and in which it can avoid being killed. Infiltration of infected tissue by

large numbers of foamy macrophages containing periodic acid–Schiff (PAS)–staining inclusions (representing ingested bacteria) is a char acteristic and most common finding. With gastrointestinal disease progression, villus atrophy, lymphangiectasia, crypt hyperplasia, and apoptosis of surface epithelial cells are observed in the small intestine, with resultant diarrhea due to decreased absorption and increased leak of water and solutes. Occasionally, involvement of lymphatic or hepatic tissue may manifest as noncaseating granulomas that can mimic sar coid or granulomatous vasculitis.

■ ■CLINICAL MANIFESTATIONS Asymptomatic Colonization/Carriage Studies using primar ily PCR have detected T. whipplei sequence in stool, saliva, duodenal tissue, and (rarely) blood in the absence of symptoms. Although prevalence rates are still being defined, in Western European countries, detection in saliva (0.2%) is less common than that in stool (1–11%) and appears to occur only with concomitant fecal carriage. The preva lence of fecal carriage is elevated among individuals with exposure to waste water or sewage (12–26%) and among children living in tropical Africa and Asia (20–48%). A duration of carriage of 7 years for the same strain has been described in a sewer worker. Evolution of the car rier state into chronic disease is uncommon. Bacterial loads are lighter in asymptomatic carriage than in active disease. Acute Infection T. whipplei has been implicated as a cause of acute gastroenteritis in children. It was also detected via PCR in the blood of 4.6% of febrile patients (75% of whom were <15 years of age) from two rural villages in Senegal as opposed to 0.25% of healthy controls. Further, T. whipplei has been implicated as a cause of acute pneumonia. These data suggest that primary acquisition may result in symptomatic pulmonary or intestinal infection or a febrile syndrome, which perhaps are more common than is generally appreciated. PART 5 Infectious Diseases Chronic Infection • “CLASSIC” WD So-called classic WD was the initial clinical syndrome recognized, with consequent identifica tion of T. whipplei. This chronic infection is defined by involvement of the duodenum and/or jejunum that develops over years. In most individuals, the initial phase of disease manifests primarily as intermit tent, often symmetrical, occasionally chronic, and rarely destructive migratory oligo- or polyarthralgias/seronegative arthritis involving the knees, wrists, ankles, and metacarpal-interphalangeal joints most commonly. Less frequently, spondylitis, sacroiliitis, discitis, tenosyno vitis, bursitis, and prosthetic hip infection also have been described. Intermittent fever, myalgias, and skin nodules may accompany joint symptoms. Tests for rheumatoid factor and antinuclear antibody are usually negative. This initial stage is often confused with a variety of rheumatologic disorders and, on average, lasts 6–8 years before gastrointestinal symptoms commence. Treatment of presumed inflam matory arthritis with immunosuppressive agents (e.g., glucocorticoids, anti-TNF-α, anakinra) can accelerate progression of the disease pro cess; thus, screening for WD prior to initiation of immunosuppres sant therapy may be appropriate, depending on the clinical scenario. Alternatively, antimicrobial therapy for another indication may reduce symptoms, and this situation should also prompt consideration of WD. The intestinal symptoms that develop in the majority of cases are characterized by diarrhea with accompanying weight loss and may be associated with fever and abdominal pain. Occult gastrointestinal blood loss, vitamin

deficiencies, hepatosplenomegaly (10–15%), and ascites (10%) are less common. Anemia and hypereosinophilia may be detected. The most common finding on abdominal computed tomography is mesenteric and/or retroperitoneal lymphadenopathy (usually raising concern about lymphoma). The endoscopic or videocapsule observation of pale, yellow, or shaggy mucosa with erythema or ulceration past the first portion of the duodenum suggests WD (Fig. 181-1). When endoscopy with duodenal biopsy is nondiagnostic, a video-capsule study may assist in identifying more distal lesions for subsequent biopsy. 18F-Fluorodeoxyglucose positron emission tomog raphy (FDG-PET) studies in patients with WD suggest the entire small bowel can be involved. Diagnostic misdirection can be caused by

FIGURE 181-1 Endoscopic view of the jejunal mucosa demonstrating a thickened, granular mucosa and “white spots” due to dilated lacteals. (Reprinted with permission from J Bureš et al: Whipple’s disease: Our own experience and review of the literature. Gastroenterol Res Pract, 2013.) co-infection with Giardia lamblia, which is occasionally identified. The intestinal phase can also be confused with Crohn or celiac disease. In addition to rheumatologic and intestinal disease, neurologic (6–63%), cardiac (17–55%), pulmonary (10–50%), lymphatic (10–55%), ocular (5–10%), dermal (5–30%), and less commonly other sites are variably involved in classic WD. Neurologic Disease CNS disease, defined by PCR-based detec tion of T. whipplei in cerebrospinal fluid (CSF), develops in ~50% of patients, many of whom are asymptomatic. A variety of neurologic manifestations have been reported and portend a poor prognosis. The most common are cognitive changes including memory impairment progressing to dementia, personality and mood alterations, hypotha lamic involvement (e.g., polyuria/polydipsia, sleep-cycle disorders), and supranuclear ophthalmoplegia. In addition, neuro-ophthalmologic manifestations of WD include supranuclear gaze palsy (usually verti cal), oculomasticatory and oculofacial myorhythmia (highly suggestive of WD), nystagmus, and retrobulbar neuritis. Focal neurologic pre sentations (dependent on lesion location), seizures, ataxia, meningitis, encephalitis, rhomobo- or limbic encephalitis, hydrocephalus, myelop athy, myoclonus, choreiform movements, and distal polyneuropathy also have been described. Neurologic sequelae occur with CNS disease, and the mortality risk is significant. Magnetic resonance imaging (MRI) results may be normal. Identified lesions (solitary or multifocal) are usually T2 and fluid-attenuated inver sion recovery (FLAIR) hyperintense and may enhance with gadolinium. All sites can be involved, and the nature of lesions is variable (e.g., nodu lar, infiltrative, tumor-like). Although imaging findings are myriad and are not diagnostic, the median temporal lobe, midbrain, hypothalamus, and thalamus are commonly affected. FDG-PET may reveal increased uptake. CSF analysis may be normal; when abnormal, leukocytosis (gen erally lymphocyte-predominant) and an elevated protein concentration are common. A low CSF glucose level has been reported. Cardiac Disease Endocarditis is increasingly recognized in WD (85% of cases in males), causes 2.6−6.3% of culture-negative endocarditis cases, and may be complicated by congestive heart failure (40% of cases), embolic events, arrhythmias, mycotic aneurysm, or rarely hypoten sion. Fever is often absent, and the Duke clinical criteria are rarely met.

Vegetations are identified by echocardiography in 50–75% of cases. All valves, alone or in combination, can be affected; most commonly involved are the aortic and mitral valves. Preexisting valvular disease is found in only a minority of cases, although infection of bioprosthetic valves has been described. Mural, myocardial, aortic (aortitis), or peri cardial disease also occurs alone or in combination with valvular involve ment. Constrictive pericarditis develops infrequently. The

diagnosis of cardiac disease is rarely made prior to surgical intervention. Pulmonary Disease Some combination of interstitial disease, nodules, parenchymal infiltrate, and pleural effusion is observed. An association with pulmonary hypertension has also been reported. The clinical significance of T. whipplei sequence identified in bronchoalveo lar lavage fluid (BALF) from asymptomatic HIV-infected individuals or in a case of interstitial lung disease is unresolved but suggests caution in diagnosing “isolated” pneumonia based on sequence alone. Notably, while the bacterium seems to exist in the airways of HIV-infected per sons at higher rates, its presence is not clearly associated with increased inflammation or a discernible decrease in lung function. Lymphatic Disease Mesenteric and retroperitoneal lymphadenopa thy are common with intestinal disease, and mediastinal adenopathy may be associated with pulmonary infection. Peripheral adenopathy is less common. Ocular Disease (Non–Neuro-Ophthalmologic) Uveitis is the most common form of ocular disease, usually presenting as a change in vision or “floaters.” Anterior (anterior chamber), intermediate (vitreous), and posterior (retina/choroid) uveitis can occur alone or in combination. Treatment with glucocorticoids alone can worsen uveitis and unmask extraocular disease. Likewise, use of local or systemic glucocorticoids after ocular surgery can precipitate ocular infection, likely as a result of asymptomatic or subclinical disease. Keratitis, crystalline keratopathy, and optic neuritis also have been reported. Patients may be misdiag nosed with sarcoid or Behçet’s disease prior to the recognition of WD. Dermatologic Disease Skin hyperpigmentation (melanoderma), particularly in light-exposed areas in the absence of adrenal dysfunction, is suggestive of WD. A variety of other cutaneous manifestations have been described, including erythematous macular lesions, nonthrombo cytopenic purpura, subcutaneous nodules, and hyperkeratosis. Miscellaneous Sites Thyroid, renal, testicular, epididymal, gall bladder, skeletal muscle, and bone marrow involvement and membra nous nephropathy have all been described. In fact, almost any organ can be involved in classic WD, with varying frequency, variable com binations, and myriad signs and symptoms. As a result, WD should be considered in the setting of a chronic multisystemic process. Despite its rarity, the combination of rheumatologic and intestinal disease with weight loss, with or without neurologic and cardiac involvement, war rants heightened suspicion. ISOLATED INFECTION This entity has been defined as infection in the absence of intestinal symptoms, although an occasional small-bowel biopsy may be PAS-positive or more commonly PCR-positive in this setting. “Isolated infection” is something of a misnomer since multiple nonintestinal sites of T. whipplei infection are not uncommon. Infec tion at the same nonintestinal sites (single or multiple) that are variably involved in classic WD may also present as “isolated infection.” Further, intestinal disease can subsequently develop. Endocarditis, neurologic disease, uveitis, rheumatologic manifestations, and pulmonary involve ment are most commonly described. Signs and symptoms are similar to those described for T. whipplei infection of these sites in classic WD. With enhanced PCR-based diagnostic capabilities, T. whipplei infection without concomitant intestinal involvement (of which endocarditis is the best example) will probably be diagnosed increasingly often. REINFECTION/RELAPSING DISEASE/IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) It has been suggested that, if an underlying host immune defect places an individual at risk for chronic infection, then that person may be at risk for reinfection due to occupational exposure or contact with family members who are

asymptomatically colonized. One case of apparent reinfection that was due to a different genotype supports this contention.

Optimal treatment regimens and durations are still being defined. However, it is clear, especially in the setting of occult or overt CNS disease, that treatment with oral tetracycline or trimethoprimsulfamethoxazole (TMP-SMX) alone may result in disease relapse. Relapses or perhaps reinfections occurring years to decades after initial therapy have been described. As in patients treated for HIV or mycobacterial disease, IRIS has been described in up to 17% of patients treated for T. whipplei infec tion. Prior immunosuppressive therapy increases the likelihood of IRIS, in which inflammation recurs after an initial clinical response to treatment and loss of PCR detection of T. whipplei. In patients with chronic WD, IRIS may be related to sustained disruption of the epithe lial barrier, leading to increased translocation of gut-derived microbial products and dysbalanced T-cell restoration. Manifestations include the development of fever, arthritis, skin lesions, subcutaneous nodules, pleuritis, uveitis, and orbital and periorbital inflammation; some cases have been fatal. ■ ■DIAGNOSIS Considering T. whipplei infection and ensuring that the appropriate tests are performed are the critical steps in making the diagnosis, which otherwise will likely be missed. Serology is of little value since patients with active infection usually mount a poor IgM/IgG response to

T. whipplei and a positive result most likely reflects prior exposure and clearance. The clinical presentation will in part dictate which clinical specimens are most likely to enable the diagnosis. In the presence (and perhaps the absence) of gastrointestinal symptoms, postbulbar duo denal biopsies should be performed, although a normal macroscopic appearance is common. As a general rule, the diagnostic yield is greater for tissue specimens than for body fluids. Biopsy of normal-appearing skin may detect T. whipplei in the setting of classic WD and serve as a minimally invasive means to establish the diagnosis. It is prudent to collect CSF even in the absence of CNS symptoms; asymptomatic disease is common, the CNS is the most common site for relapse, and thus the information gained by CSF examination could influence the design and duration of the treatment regimen. CHAPTER 181 Whipple Disease The diagnosis of classic WD was originally based on histologic find ings in intestinal biopsy specimens. Although this diagnostic procedure remains important, it is not optimally sensitive. Infiltration of the lamina propria with macrophages containing PAS-positive inclusions that are resistant to diastase is observed. However, PAS is nonspecific, also yield ing positive results with mycobacteria as well as other microorganisms. Staining of other tissues or fluids (e.g., ocular aspirations) for PASpositive inclusions in macrophages can be performed to support the diagnosis. The sensitivity of identification of PAS-positive inclusions in WD may be decreased by anti-TNF-α therapy. Electron microscopy can be used to identify the trilaminar cell wall of T. whipplei. When available, immunohistochemistry has greater specificity and sensitivity than PAS staining and can be performed on archived fixed tissue. Alternatively, the use of fluorescence in situ hybridization (FISH) has been reported as a complementary diagnostic tool with various tissue samples. The development and implementation of specific PCR-based diag nostics have significantly increased the sensitivity and specificity of

T. whipplei identification. PCR can be applied to affected tissues (with greater sensitivity for non-formalin-fixed than for formalin-fixed tis sue) in support of histologic findings and to various body fluids. It is important to note that the interpretation of a PCR-based diagnostic approach must take into account limitations such as false-positive results due to sample contamination, false-negative results due to low organism load, poor sample quality, inadequate DNA extraction, and variability in performance of various PCR assays. Quantitative com parisons from different sites can add specificity to PCR-based diagnos tics of WD and distinguish between WD patients and

asymptomatic carriers. In patients suspected of having WD, PCR testing of duo denal biopsy specimens with a cycle threshold value of ≤30 can help confirm the diagnosis, even in cases with negative PAS staining. As with all diagnostic tests, consideration of pretest probability is critical

for interpretation, and a negative result does not exclude WD. Urine PCR for T. whipplei infection may hold promise for the noninvasive diagnosis of classic and isolated WD. In one study of 12 cases, urine PCR was positive in nine cases (75%) prior to treatment compared to zero (0%) of 110 controls, including 11 controls that were presumed carriers in whom feces PCR was positive, although there was no evi dence of disease. In addition, urine PCR is a potential tool to evaluate the success of WD therapy. Saliva and fecal PCR are inappropriate as the sole diagnostic tools for WD due to low positive predictive values, which more commonly identify colonization, not disease; a positive result requires confirmation from an appropriate end-organ tissue or body fluid.

Next-generation sequencing techniques to evaluate for cell-free DNA (cfDNA) in plasma may lead to increased recognition of T. whipplei as a cause of endocarditis. T. whipplei has been successfully cultured from blood, CSF, synovial fluid, BALF, valve tissue, duodenal tissue, skeletal muscle, and lymph nodes, but culture is not practical since it takes months to obtain a positive result. Affected anatomic sites in WD patients may demonstrate uptake on FDG-PET, which in turn could guide tissue sampling for use in specific tests. TREATMENT Whipple Disease Data on treatment are emerging, but the optimal regimen and dura tion for chronic infection, which may depend on the sites involved (e.g., CNS and heart valve), are unclear. Appropriate treatment usu ally results in a rapid—and at times remarkable—clinical response (e.g., in CNS disease), but eradication requires prolonged treat ment. Maintenance of a durable response has been more challeng ing because of both relapse and host predisposition to reinfection. PART 5 Infectious Diseases Rates of relapse, particularly of CNS disease, were unacceptable with oral tetracycline or TMP-SMX monotherapy. Sequence data now indicate that TMP is not active against T. whipplei (given the absence of dihydrofolate reductase in T. whipplei) and that resistance to SMX and sulfadiazine can occur. However, a randomized controlled trial in 40 patients, who received either ceftriaxone (2 g IV q24h) or merope nem (1 g IV q8h) for 2 weeks followed by oral TMP-SMX (160/800 mg)

twice a day for 1 year, demonstrated outstanding efficacy. The only case in which therapy failed—an asymptomatic CNS infection that was not eradicated by either regimen—was subsequently cured with oral minocycline and chloroquine (250 mg/d after a loading dose). A follow-up trial reported similar efficacy with a regimen of cef triaxone (2 g IV q24h) for 2 weeks followed by oral TMP-SMX for

3 months. One issue in these trials was that the doses—and perhaps the duration of ceftriaxone and meropenem treatment as well—were not optimal for CNS infection. By contrast, in a small retrospective series, outcome was better in patients treated with oral doxycycline (100 mg twice a day) plus hydroxychloroquine (200 mg three times a day to raise phagosome pH and increase drug activity in vitro) than in patients initially treated with TMP-SMX. Until more data become available, it seems prudent—at least in asymptomatic/symptomatic CNS disease (which is present in many cases of WD)—first to administer CNS-optimized doses of IV ceftriaxone (2 g q12h) or meropenem (2 g q8h) for 2–4 weeks and then to treat with oral doxycycline, or minocycline plus hydroxy chloroquine for at least 1 year, if tolerated. Although TMP-SMX has been frequently used as the oral alternative with reported success, a number of relapses or reinfections with TMP-SMX treatment

have been reported, thereby suggesting caution for its use in patients with infection in critical locations such as the CNS and the heart. Although data on the use of PCR to guide therapy do not exist, it seems reasonable that continued T. whipplei detection by PCR, especially in the CSF and perhaps urine, should dictate at least continuation of therapy or perhaps consideration of an alternative regimen when in conjunction with a poor clinical response.

Timely recognition may result in cure with medical manage ment alone. Surgery may be needed in the setting of endocarditis with significant valve dysfunction or myocardial abscess. Current European guidelines for the treatment of endocarditis caused by

T. whipplei recommend oral doxycycline plus hydroxychloroquine for ≥18 months or, alternatively, ceftriaxone (2 g q24h IV) or peni cillin (2 million units q4h IV) plus streptomycin (1 g q24h IV) for 2–4 weeks followed by oral TMP-SMX (800 mg q12h); a small study from Spain reported that treatment durations of 12–13 months with these regimens or variations were efficacious. Data on isolated infection and certain site-specific treatment issues are even more limited. Anecdotal reports describe suc cessful treatment of uveitis with oral TMP-SMX with or without rifampin, whereas treatment with tetracycline alone has resulted in relapse. Although a role for adjunctive intraocular therapy has been reported, the data are unclear on this point. There is a single case report of clearance of infection in a chronically relapsing patient by the addition of interferon gamma to antimicrobials; supplementa tion to antimicrobials may be a consideration to address refractory disease or potential issues with antibiotic resistance. Although data on the treatment of foreign body–associated infection are virtually nonexistent, medical treatment for a pros thetic hip infection was apparently successful; however, follow-up was limited. The occurrence of a Jarisch-Herxheimer reaction within 24 h of treatment initiation has been described, with rapid resolution. The addition of glucocorticoids may be beneficial in the management of IRIS, and thalidomide has been used in steroid-refractory cases. Importantly, although data are lacking, due to the inherent risk of relapse or reinfection, lifelong suppressive therapy with doxy cycline after completion of the initial treatment regimen has been advocated. Regardless of the therapeutic approach chosen, an effort to ensure compliance and close follow-up for potential relapse or reinfection, which can occur many years after an apparent cure, will maximize the chances for a good outcome. PREVENTION Attempts are underway to develop a peptide-based vaccine against T. whipplei. However, the role for this may be limited given the rela tive rarity of infection. ■ ■FURTHER READING Bally JF et al: Systematic review of movement disorders and oculomo tor abnormalities in Whipple’s disease. Mov Disord 33:1700, 2018. Boumaza A et al: Whipple’s disease and Tropheryma whipplei infec tions: From bench to bedside. Lancet Infect Dis 22:e280, 2022. Crews NR et al: Diagnostic approach for classic compared with local ized Whipple disease. Open Forum Infect Dis 5:ofy136, 2018. Damaraju D et al: Clinical problem-solving: A surprising cause of chronic cough. N Engl J Med 373:561, 2015. de Vries CR et al: 710. Non-invasive diagnosis of Whipple endocardi tis using next-generation sequencing for microbial cell-free DNA in plasma. Open Forum Infect Dis 7:S407, 2020. Guérin A et al: IRF4 haploinsufficiency in a family with Whipple’s disease. Elife 7:e32340, 2018. Gunther U et al: Gastrointestinal diagnosis of classical Whipple disease: Clinical, endoscopic, and histopathologic features in 191 patients. Medicine 94:e714, 2015. Ioannou P et al: Whipple’s disease-associated infective endocarditis: A systematic review. Infect Dis (Lond) 55:447, 2023. Lagier JC, Raoult D: Whipple’s disease and Tropheryma whipplei infections: When to suspect them and how to diagnose and treat them. Curr Opin Infect Dis 31:463, 2018. Meyer S et al: Contribution of PCR to differential diagnosis between patients with Whipple disease and Tropheryma whipplei carriers. J Clin Microbiol 61:e0145722, 2023. Moter A et al: Potential role for urine polymerase chain reaction in the

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