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. Postoperative acute or chronic ocular Whipple's disease has been described in association with local or systemic glucocorticoid use; its detection in this setting raises the possibility that asymptomatic or subclinical disease has been unmasked. Keratitis and crystalline keratopathy also have been reported. Patients may be misdiagnosed with sarcoid or Behçet's disease prior to the recognition of Whipple's.

Dermatologic disease Skin hyperpigmentation, particularly in light-exposed areas in the absence of adrenal dysfunction, should be suggestive of Whipple's disease. A variety of other cutaneous manifestations have been described, including erythematous macular lesions, nonthrombocytopenic purpura, subcutaneous nodules, and hyperkeratosis.

Miscellaneous sites Thyroid, renal, testicular, epididymal, gallbladder, skeletal muscle, and bone marrow involvement have all been described. In fact, almost any organ can be involved in classic Whipple's disease, with varying frequency, variable combinations, and myriad signs and symptoms. As a result, Whipple's disease 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, warrants 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 PCR-positive in this setting. "Isolated infection" is something of a misnomer since multiple nonintestinal sites of *T. whipplei* infection are not uncommon. Infection at the same nonintestinal sites (single or multiple) that are variably involved in classic Whipple's disease may also present as "isolated infection." Endocarditis, neurologic disease, uveitis, rheumatologic manifestations, and pulmonary involvement are most commonly described. Signs and symptoms are similar to those described for *T. whipplei* infection of these sites in classic Whipple's disease. 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 relapse 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 trimethoprim-sulfamethoxazole (TMP-SMX) alone may result in disease relapse.

As in patients treated for HIV or mycobacterial disease, IRIS has been described in patients treated for *T. whipplei* infection. 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*. Manifestations include fever, arthritis, skin lesions, pleuritis, uveitis, and orbital and periorbital inflammation.

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. 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 duodenal biopsies should be performed. As a general rule, 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 Whipple's disease and serve as a minimally invasive means to establish the diagnosis. It is unclear whether CSF should be obtained in the absence of CNS symptoms, but its collection should be considered: the CNS is the most common site for relapse, and thus the information gained by CSF examination could influence the design of the treatment regimen.

The development and implementation of PCR-based diagnostics have significantly increased the sensitivity and specificity of *T. whipplei* identification. PCR can be applied to affected tissues (fixed and nonfixed) and various body fluids (e.g., CSF; aqueous or vitreous humor; joint, pericardial, or pleural fluid; BALF; blood; feces). In some clinical scenarios, a generic 16S rRNA bacterial assay combined with amplicon sequencing can be used to detect and identify *T. whipplei* sequence. Delineation of the *T. whipplei* genomic sequence has enabled the development and broad availability of more sensitive and specific PCR-based assays. The interpretation of a PCR-based diagnostic approach must take into account limitations such as false-positive results due to sample contamination and false-negative results due to organism load, sample quality, and inadequate DNA extraction.

The diagnosis of classic Whipple's disease was originally based on histologic findings in intestinal biopsy specimens, and this diagnostic procedure remains important. Infiltration of the lamina propria with macrophages containing inclusions (representing ingested bacteria) that are positive on periodic acid–Schiff (PAS) staining and resistant to diastase is observed. However, PAS is nonspecific, also yielding positive results with mycobacteria (which can be differentiated with Ziehl-Neelsen stain), *Rhodococcus equi*, *Bacillus cereus*, *Corynebacterium* species, and *Histoplasma* species. *T. whipplei* can also be detected by silver stain, Brown-Brenn (weakly positive), or acridine orange and is not stained by calcofluor. Staining of other tissues or fluids (e.g., ocular aspirations) for PAS-positive inclusions in macrophages can be performed to support the diagnosis. 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. *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. Likewise, serology is of limited value for the diagnosis of Whipple's disease because the prevalence of exposure is much higher than that of chronic disease development and the antibody response to *T. whipplei* appears to be blunted in the disease state.

Although histologic or cytologic detection of *T. whipplei* is less specific and sensitive than PCR, a positive result is strongly supportive within the appropriate clinical context and is definitive when combined with a more specific test (e.g., PCR, immunohistochemistry).

TREATMENT WHIPPLE'S DISEASE

Data on treatment are emerging, but questions persist regarding the optimal regimen and duration, which may depend on the site of infection (e.g., CNS and heart valve). Appropriate treatment usually results in a rapid and at times remarkable clinical response (e.g., in CNS disease). Maintenance of a durable response has been more challenging.

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* due to the absence of dihydrofolate reductase, but this drug was used extensively before this fact was known. This information prompted a randomized controlled trial in 40 patients, who received either ceftriaxone (2 g IV q24h) or meropenem (1 g IV q8h) for 2 weeks followed by oral TMP-SMX (160/800 mg) twice a day for 1 year. The efficacy of these regimens was outstanding. The only instance of therapy failure—in a case of asymptomatic CNS infection that was