TABLE 200-1 APPROPRIATE AND INAPPROPRIATE ANTIBIOTIC THERAPY FOR ACTINOMYCOSIS[a]

Category	Agent
Extensive successful clinical experience[b]	Penicillin: 3–4 million units IV q4h[c]
	Amoxicillin: 500 mg PO q6h
	Erythromycin: 500–1000 mg IV q6h or 500 mg PO q6h
	Tetracycline: 500 mg PO q6h
	Doxycycline: 100 mg IV or PO q12h
	Minocycline: 100 mg IV or PO q12h
	Clindamycin: 900 mg IV q8h or 300–450 mg PO q6h
Anecdotal successful clinical experience	Ceftriaxone[c]
	Ceftizoxime
	Imipenem-cilastatin
	Piperacillin-tazobactam
Agents that should be avoided	Metronidazole
	Aminoglycosides
	Oxacillin
	Dicloxacillin
	Cephalexin
Agents predicted to be efficacious on the basis of in vitro activity	Moxifloxacin
	Vancomycin
	Linezolid
	Quinupristin-dalfopristin
	Ertapenem[c]
	Azithromycin[c]

[a]Additional coverage for concomitant "companion" bacteria may be required. [b]Controlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximal parenteral antimicrobial dose for 2–6 weeks followed by oral therapy, for a total duration of 6–12 months, is required for serious infections and bulky disease, whereas a shorter course may suffice for less extensive disease, particularly in the oral-cervicofacial region. Monitoring the impact of therapy with CT or MRI is advisable when appropriate. [c]These agents can be considered for at-home parenteral therapy; penicillin requires a continuous infusion pump.

by which to accomplish this goal. A similar approach is reasonable for immunocompromised patients, although refractory disease has been described in HIV-infected individuals. Although the role played by "companion" microbes in actinomycosis is unclear, many isolates are pathogens in their own right, and a regimen covering these organisms during the initial treatment course is reasonable.

Combined medical-surgical therapy is still advocated in some reports. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease. CT and MRI should be used to monitor the response to therapy. In most cases, either surgery can be avoided or a less extensive procedure can be used. This approach is particularly valuable in sparing critical organs, such as the bladder or the reproductive organs in women of childbearing age. For a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach. When a critical location is involved (e.g., the epidural space, the CNS), when there is significant hemoptysis, or when suitable medical therapy fails, surgical intervention may be appropriate. In the absence of optimal data, the combination of a prolonged course of antimicrobial therapy and resection—at least of necrotic bone for bisphosphonate-related osteonecrosis of the jaw (BRONJ)—is a reasonable approach.

WHIPPLE'S DISEASE

Whipple's disease, a chronic multiorgan infection caused by *Tropheryma whipplei*, was first described in 1907. The long-held belief that Whipple's disease 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 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 (Whipple's disease) is a rare development after exposure. "Classic" Whipple's disease is manifested variably by a combination of arthralgias/arthritis, weight loss, chronic diarrhea, abdominal pain, and fever; less commonly, involvement at sites other than the gastrointestinal tract is documented. Acute infection and chronic organ disease in the absence of intestinal involvement (see "Isolated Infection," below) are described with increasing frequency. Since untreated Whipple's disease is often fatal and delayed diagnosis may lead to irreparable organ damage (e.g., in the CNS), knowledge of the clinical scenarios in which Whipple's 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. A genotyping scheme based on a variable region has disclosed more than 70 genotypes (GTs) to date. GTs 1 and 3 are most commonly reported, but all GTs appear to be capable of causing similar clinical syndromes.

EPIDEMIOLOGY

Whipple's disease is rare but has been increasingly recognized since the advent of PCR-based diagnostic tools. It occurs in all parts of the globe, with an incidence presently estimated at 1 case per 1 million patient-years. Seroprevalence studies indicate that ~50% of Western Europeans and ~75% of Africans from rural Senegal have been exposed to *T. whipplei*. A predilection for chronic disease has been observed in middle-aged Caucasian men. Males are infected five to eight times more frequently than females. 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 pattern suggesting fecal-oral spread. Recent data support oral-oral or fecal-oral spread among family members. Further, the development of acute *T. whipplei* pneumonia in children raises the possibility of droplet or airborne transmission.

PATHOGENESIS AND PATHOLOGY

Since rates of exposure to *T. whipplei* appear to be much higher (e.g., ~50% in Western Europe, as stated above) than rates of chronic disease development (0.00001%), it has been hypothesized that chronically infected individuals possess a subtle host-defense abnormality that does not place them at risk for non–*T. whipplei* infection. The HLA alleles DRB1*13 and DQB1*06 may be associated with an increased risk of infection. Chronic infection results in a general state of immunosuppression characterized by low CD4+ T cell counts, high levels of interleukin 10 production, increased activity of regulatory T cells, alternative activation of macrophages with diminished antimicrobial activity (M2 polarization) and ensuing apoptosis, and blunted development of *T. whipplei*–specific T cells. Immunosuppressive glucocorticoid treatment or anti–tumor necrosis factor α therapy appears to accelerate progression of disease. Recently, asymptomatic HIV-infected individuals were found to have significantly higher levels of *T. whipplei* sequence in bronchoalveolar lavage fluid (BALF) than did non-HIV-infected individuals, and these levels decreased