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 ceftriaxone (2 g IV q24h) for 2 weeks followed by oral TMP-SMX for 3 months. One issue in these trials was that the CNS doses—and perhaps the duration of ceftriaxone and meropenem treatment as well—were not optimal. Further, investigators have speculated that oral regimens with greater CNS penetrance, such as sulfadiazine (2–4 g/d in 3 or 4 divided doses) and/or doxycycline or minocycline (200 mg/d in 2 divided doses) plus hydroxychloroquine (200 mg three times a day, to raise phagosome pH and increase drug activity in vitro), might render the parenteral phase of treatment unnecessary, given that the one failure of therapy for CNS disease was cured with a similar regimen. Another issue is concern about the potential development of resistance to sulfa drugs. Lastly, it is unclear whether oral sulfa- or tetracycline-based regimens will suffice in endocarditis. Until more data become available, it seems prudent—at least in asymptomatic/symptomatic CNS disease or cardiac infection—to administer CNS-optimized doses of IV ceftriaxone (2 g q12h) or meropenem (2 g q8h) for at least 2 weeks followed by oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for at least 1 year, if tolerated. 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, should dictate at least continuation of therapy and perhaps consideration of an alternative regimen.

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 clearly documented IRIS.

Data on certain site-specific treatment issues are even more limited. Anecdotal reports describe successful 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. Surgery may be needed in the setting of endocarditis with significant valve dysfunction; however, timely recognition can result in cure with medical management alone. Although data on the treatment of foreign body–associated infection are virtually nonexistent, medical treatment for a prosthetic hip infection was apparently successful; however, follow-up was limited.

Regardless of the therapeutic regimen chosen, an effort to ensure compliance and close follow-up for potential relapse (or perhaps reinfection), which can occur many years after an apparent cure, will maximize the chances for a good outcome.

201 Infections Due to Mixed Anaerobic Organisms

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Anaerobes comprise the predominant class of bacteria of the normal human microbiota (formerly termed "the normal human flora") that reside on mucous membranes and predominate in many infectious processes, particularly those arising from mucosal surfaces. These organisms generally cause disease subsequent to the breakdown of mucosal barriers and the leakage of the microbiota into normally sterile sites. Infections resulting from contamination by the microbiota are usually polymicrobial and involve both aerobic and anaerobic bacteria. However, the difficulties encountered in handling specimens in which anaerobes may be important and the technical challenges entailed in cultivating and identifying these organisms in clinical microbiology laboratories continue to leave the anaerobic etiology of an infectious process unproven in many cases. Therefore, an understanding of the types of infections in which anaerobes can play a role is crucial in selecting appropriate microbiologic tools to identify the organisms in clinical specimens and in choosing the most appropriate treatment, including antibiotics and surgical drainage or debridement of the infected site.

This chapter focuses on infections caused by nonsporulating anaerobic bacteria. It does not address clostridial infections and syndromes, which are covered elsewhere (Chaps. 161 and 179).

DEFINITIONS

Anaerobic bacteria are organisms that require reduced oxygen tension for growth, failing to grow on the surface of solid media in 10% CO_2 in air. (In contrast, *microaerophilic bacteria* can grow in an atmosphere of 10% CO_2 in air or under anaerobic or aerobic conditions, although they grow best in the presence of only a small amount of atmospheric oxygen, and *facultative bacteria* can grow in the presence or absence of air). Most clinically relevant anaerobes, such as *Bacteroides fragilis, Prevotella melaninogenica*, and *Fusobacterium nucleatum*, are relatively aerotolerant. Although they can survive for sustained periods in the presence of up to 2–8% oxygen, they generally do not multiply in this environment. A smaller number of pathogenic anaerobic bacteria (which are also part of the microbiota) die after brief contact with oxygen, even in low concentrations.

ANAEROBES OF THE HUMAN MICROBIOTA

Most human mucocutaneous surfaces harbor a rich indigenous normal microbiota composed of aerobic and anaerobic bacteria. These surfaces are dominated by anaerobic bacteria, which often account for 99.0–99.9% of the culturable microbiota and range in concentration from 10^9/mL in saliva to 10^{12}/mL in gingival scrapings and the colon. It is interesting that anaerobes inhabit many areas of the body that are exposed to air: skin, nose, mouth, and throat. Anaerobes are thought to reside in the portions of these sites that are relatively well protected from oxygen, such as gingival crevices. New technologies based on analyses of microbial DNA have expanded our knowledge of these bacterial populations. For example, in an analysis of 13,555 prokaryotic ribosomal RNA gene sequences from the colon, most bacteria identified were considered uncultivated and novel microorganisms. Two immense projects based on these new technologies, the Human Microbiome Project funded by the U.S. National Institutes of Health and MetaHIT financed by the European Commission, aim to characterize the normal microbiota of healthy individuals.

The major reservoirs of anaerobic bacteria are the mouth, lower gastrointestinal tract, skin, and female genital tract (Table 201-1). In the oral cavity, the ratio of anaerobic to aerobic bacteria ranges from 1:1 on the surface of a tooth to 1000:1 in the gingival crevices. *Prevotella* and *Porphyromonas* species comprise much of the indigenous oral anaerobic microbiota. *Fusobacterium* and *Bacteroides* (non–*B. fragilis* group) are present in lower numbers. Anaerobic bacteria are not found in appreciable numbers in the normal stomach and upper small intestine. In the distal ileum, the microbiota begins to resemble that of the colon. In the colon, the ratio of anaerobes to facultative species is high; for example, there are 10^{11}–10^{12} organisms/g of stool, and >99% of these organisms are anaerobic, with an anaerobe-to-aerobe ratio of ~1000:1. The predominant anaerobes in the human intestine belong to the phyla Bacteroidetes and Firmicutes and include a number of *Bacteroides* species (e.g., members of the *B. fragilis* group, such as *B. fragilis, B. thetaiotaomicron, B. ovatus, B. vulgatus, B. uniformis*, and *Parabacteroides distasonis*) as well as various clostridial, peptostreptococcal, and fusobacterial species. In the female genital tract, there are ~10^9 organisms/mL of secretions, with an anaerobe-to-aerobe ratio of 1:1 to 10:1. The predominant anaerobes in the female genital tract are *Prevotella, Bacteroides, Fusobacterium, Clostridium*, and the anaerobic *Lactobacillus* species.