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Infections Due to Mixed Anaerobic Organisms Anaerobes constitute the predominant class of bacteria of the normal human microbiota that reside on mucous membranes and predomi nate 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 anaerobic bacteria other than Clostridium species, which are covered elsewhere (Chaps. 139 and 159). ■ ■HISTORIC PERSPECTIVE Anaerobic organisms were first identified by Antonie van Leeuwen hoek in 1680—nearly a century before oxygen itself was discovered. Leeuwenhoek set up culture medium (crushed pepper powder and clean rainwater) in two glass tubes—one open to ambient air and the other sealed closed—that he incubated for several days. Although he did not expect to observe anything in the sealed tube, he was surprised to find “animalcules” in both tubes. He noted that these bacteria in the sealed tube were “bigger than the biggest sort” in the tube left open to air. It was not until the mid- to late nineteenth century that Leeuwen hoek’s findings were confirmed by Pasteur and others. However, these principles described by Leeuwenhoek underlie the basic pathogenesis of anaerobic infections: development of an anaerobic environment in a closed space is due to consumption of oxygen by aerobic organisms and results in the outgrowth of anaerobic organisms. ■ ■DIFFERENCES BETWEEN ANAEROBIC AND AEROBIC ORGANISMS Anaerobic bacteria can be categorized as obligate anaerobes (killed in the presence of ≥0.5% oxygen), aerotolerant organisms (can tolerate the presence of oxygen but cannot use it for growth), and facultative anaer obes (can grow in the presence or absence of oxygen). Most clinically relevant anaerobes,

such as Bacteroides fragilis, Prevotella melaninogenica, and Fusobacterium nucleatum, are relatively aerotolerant. These organ isms contrast with obligate aerobes, which require high concentrations of oxygen for growth, and microaerophilic organisms, which are dam aged by atmospheric concentrations of oxygen (~21%) but require low concentrations of oxygen (typically 2–10%) for growth. Given that molecular oxygen can reduce to superoxide (O_2^-) and hydrogen peroxide (H_2O_2), which are damaging to cells, the ability to tolerate the presence of oxygen is due, in part, to the expression of superoxide dis mutase and catalase. The variation in anaerobic organisms tolerating anywhere from <0.5 to 8% O_2 may reflect the amount of these enzymes that is produced. Furthermore, aerobic and anaerobic organisms differ in their energy metabolism. Cellular respiration requires establishment of an electrochemical gradient across the membrane, resulting in an electric potential (often related to a proton gradient) across the membrane. In aerobic respiration, electrons are shuttled through an electron transport chain, with oxygen as the final electron acceptor. Anaerobic organisms can metabolize energy by either anaerobic respiration or fermentation.

Given that the final electron acceptor in anaerobic respiration (e.g., sulfate, nitrate, carbon dioxide, or fumarate) is not as highly oxidizing as oxygen, this pathway is less efficient than aerobic respiration and produces less ATP per glucose molecule. In contrast, fermentation does not use an electrochemical gradient. Rather, it releases energy from an organic molecule (e.g., pyruvate and its derivatives) via substrate-level phosphorylation and is therefore a less efficient process than either aerobic or anaerobic respiration; for comparison, fermentation results in ~5% of the energy released by aerobic respiration. For these reasons, facultative anaerobes will preferentially utilize oxygen if it is available; in oxygen-limiting situations, organisms will use anaerobic respiration rather than fermentative processes, if possible.

■ ■ANAEROBES OF THE HUMAN MICROBIOTA Most human mucocutaneous surfaces harbor a rich indigenous nor mal microbiota composed of aerobic and anaerobic bacteria. These surfaces are dominated by anaerobic bacteria, which often account for 99.0–99.9% of the cultivable microbiota and range in concentration from 103/mL in the nose to 1012/mL in gingival scrapings and the colon (Table 182-1). It is interesting that anaerobes inhabit many areas of the body that are exposed to air: skin, nose, mouth, and throat. Anaer obes are thought to reside in the portions of these sites that either are relatively well protected from oxygen (e.g., gingival crevices) or have a local anaerobic environment conferred by neighboring aerobic organ isms (e.g., tooth surfaces). The ability to cultivate these organisms is improving, and—with strict attention to anaerobic conditions—more than 80% of the microscopic counts in fecal samples can be cultured. However, culture-independent approaches (e.g., sequencing of the 16S rDNA gene) show that the overwhelmingly diverse low-abundance bacterial species present in the microbiota remain uncultivated. Several projects, including the Human Microbiome Project (funded by the U.S. National Institutes of Health) and MetaHIT (financed by the European Commission), have characterized the normal microbiota of healthy individuals and have demonstrated the presence of >10,000 different bacterial species in the collective human microbiota. The human gut CHAPTER 182 Infections Due to Mixed Anaerobic Organisms TABLE 182-1 The Anaerobic Human Microbiota: An Overview ANAEROBIC/ AEROBIC RATIO POTENTIAL PATHOGEN(S) TOTAL BACTERIAa ANATOMIC SITE Nose 103–104 2:1 Peptostreptococcus spp., Prevotella spp. Oral cavity Saliva 108–109 10:1 Fusobacterium nucleatum, Prevotella melaninogenica, Prevotella oralis group, Bacteroides ureolyticus group, Peptostreptococcus spp. Tooth surface 1010–1011 1:1 Gingival crevices

1011–1012 103:1 Gastrointestinal tract Stomach 100–103 1:10 Lactobacillus spp. Duodenum 101–105 1:1 Lactobacillus spp., Streptococcus spp. Jejunum 103–106 1:1 Streptococcus spp., Lactobacillus spp., Peptostreptococcus spp. Ileum 104–109 10:1 Bacteroides spp., Streptococcus spp., Enterococcus spp. Cecum and colon 1011–1012 103:1 Bacteroides spp. (principally members of the B. fragilis group), Prevotella spp., Clostridium spp. Female genital tract 107–109 10:1 Peptostreptococcus spp., Bacteroides spp., Prevotella bivia Skin 104–106 100:1 Cutibacterium acnes aPer gram or milliliter.

alone harbors >1000 bacterial species, with 100–200 species present in any given individual.

The major reservoir of anaerobic bacteria is the lower gastrointesti nal tract, but these organisms are also present in considerable numbers in the oral cavity, skin, and female genital tract (Table 182-1). 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 make up much of the indigenous oral anaerobic microbiota. Fusobacterium and Bacteroides (non–B. fragilis group) species are present in lower numbers. Anaerobic bacteria are not found in appreciable numbers in the normal stomach and proximal small intestine. In the distal ileum, the microbiota begins to resemble that of the colon, where the ratio of anaerobes to aerobic species is high (~1000:1). The predominant anaerobes in the human intestine belong to the phyla Bacteroidetes and Firmicutes and include a number of Prevotella and 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 Clos tridium, Peptostreptococcus, Blautia, and Fusobacterium species. In the female genital tract, there are ~109 organisms/mL of secretions, with an anaerobe-to-aerobe ratio of ~10:1. The predominant anaerobes in the female genital tract are Prevotella, Bacteroides, Fusobacterium, Clos tridium, and the anaerobic Lactobacillus species. The skin microbiota contains anaerobes as well; Cutibacterium acnes (which was previously Propionibacterium acnes and will be considered as one of the Propioni bacterium species for the remainder of this chapter) is the predominant species, and other species of propionibacteria and peptostreptococci are present in lower numbers. PART 5 Infectious Diseases ■ ■ANAEROBES AND HUMAN HEALTH Commensal anaerobes have been implicated as crucial mediators of physiologic, metabolic, and immunologic functions in the mammalian host. The intestinal microbiota is essential for fermenting dietary car bohydrates into forms that are more usable by the host, among which polysaccharides are the most abundant biologic source of energy. Of the organisms found within the intestines, Bacteroides species express the widest array of polysaccharide-degrading enzymes, providing important nutrients for both the host and other commensal organisms. For example, B. thetaiotaomicron expresses 172 glycosyl hydrolases. The anaerobic intestinal microbiota is also responsible for the produc tion of secreted products that promote human health (e.g., vitamin K and bile acids useful in fat absorption and cholesterol regulation). One of the most important roles that anaerobes serve as components of the normal colonic microbiota is the promotion of resistance to colonization. The presence of commensal bacteria effectively interferes with colonization by potentially pathogenic bacterial species through the depletion of oxygen and nutrients, the production of enzymes and toxic end products, and the modulation of the host’s intestinal innate immune response. For example, the normal intestinal microbiota plays an important role in protection against enteric infections, including those due to Salmonella enterica serotype Typhimurium and Clostridium difficile. The anaerobic intestinal microbiota also has immunomodulatory properties that help regulate the immune system. The first example of this role was demonstrated with B. fragilis, which

can balance the effector functions of T cells in the peripheral immune system and induce colonic regulatory T cells via expression of polysaccharide A (PSA). Moreover, B. fragilis expresses a glycosphingolipid that regu lates the number of colonic invariant natural killer T cells. There are now numerous examples of commensal anaerobes that can modulate different aspects of the intestinal and extraintestinal immune system— everything from specific effector T cells to dendritic cells to antimicro bial peptides. Clearly, the gut microbiota confers many benefits, and its dysregula tion may play a role in the pathogenesis of diseases characterized by inflammation and aberrant immune responses, such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, asthma, and type 1 diabetes. Furthermore, the gut microbiota has been associated with obesity and metabolic syndrome. A more complete discussion of

the intersection between the microbiota and human health is covered elsewhere (Chap. 484). ■ ■ETIOLOGY There are >10,000 species of bacteria—the overwhelming majority of which are anaerobes—in the human microbiota, with each individual colonized by hundreds of species. Anaerobic infections occur when the harmonious relationship between the host and the host's microbiota is disrupted. Any site in the body is susceptible to infection with these indigenous organisms if they are introduced into otherwise sterile tis sue, either through disruption of mucosal surfaces (e.g., intestinal per foration, ischemia, surgery) or via direct inoculation of organisms into tissue (e.g., bite wounds, trauma). Because the sites that are colonized by anaerobes contain many species of bacteria, the resulting infections are often polymicrobial, involving multiple species of anaerobes in combination with synergistically acting facultative and/or microaero philic organisms. Despite the complex array of bacteria in the normal microbiota, relatively few genera are isolated commonly from human infections (Fig. 182-1). While the specific organisms identified vary with the site and source of infection, the etiologic agents typically reflect the neighboring microbiota. For example, organisms normally found in the oro- and nasopharyngeal microbiota (e.g., P. melaninogenica, Fusobacterium necrophorum, F. nucleatum, Peptostreptococcus species, Porphyromonas gingivalis, Porphyromonas asaccharolytica, and Actino myces species) can cause disease in contiguous areas, including odon togenic infections, peripharyngeal space infections, chronic sinusitis, and pleuropulmonary infections. In female genital tract infections, organisms normally colonizing the vagina (e.g., Prevotella bivia and Prevotella disiens) are the most common isolates. Escherichia coli and B. fragilis, both of which are components of the intestinal microbiota, are the most commonly identified isolates from intraabdominal abscesses. Indeed, the B. fragilis group, which encompasses 25 species and includes B. thetaiotaomicron, B. vulgatus, B. uniformis, and B. ovatus, contains the anaerobic organisms among the most frequently isolated from clinical infections. It is useful to think about anaerobic infectious etiologies with regard not only to their anatomic location but also to their microbiologic features. While many anaerobic gram-negative bacilli cause disease (e.g., Prevotella, Bacteroides, Fusobacterium, and Porphyromonas species), Veillonella species, which are part of the oral and intestinal microbiota, are among the few anaerobic gram-negative cocci that have been impli cated in human disease. Similarly, the peptostreptococci (e.g., P. micros, P. asaccharolyticus, and P. anaerobius) and Finegoldia magnus (which was previously Peptostreptococcus magnus and will be considered as part of the peptostreptococci for the remainder of this chapter) are the chief anaerobic gram-positive cocci that have pathogenic potential. Clostridium species are the primary anaerobic spore-forming grampositive rods that produce human disease (Chap. 159). Uncommonly, anaerobic gram-positive non-spore-forming bacilli cause infection;

Gram-positive cocci Clostridium spp. Other Gram-positive rods Bacteroides fragilis Other Bacteroides spp. Prevotella spp. Fusobacterium spp. Porphyromonas spp. Other Gram-negative rods Veillonella spp. FIGURE 182-1 Distribution of anaerobic organisms isolated from clinical materials. (Data combined from Y Park et al: Clinical features and prognostic factors of anaerobic infections: A 7-year retrospective study. Korean J Intern Med 24:13, 2009; and Japanese Association for Anaerobic Infections Research: Anaerobic infections (general): Epidemiology of anaerobic infections. J Infect Chemother 17:4, 2011.)

C. acnes, a component of the skin microbiota and a cause of foreignbody infections, and Actinomyces species are relevant examples. ■ ■PATHOGENESIS First and foremost, anaerobic infections require an anaerobic environ ment with a lowered oxidation-reduction potential. In some circum stances, this environment can occur directly—e.g., in tissue ischemia, trauma, surgery, or a perforated viscus. In many other situations, the infection is polymicrobial, and the facultative organisms maintain a lowered oxidation-reduction potential in the local microenvironment that allows for the propagation of obligate anaerobes. Once the proper anaerobic environment is established, the organisms must still contend with the host's immune defenses. Similar to aerobic organisms, anaer obes express an array of virulence factors that help evade host defenses, they can form abscesses as a protective measure, and they can act syn ergistically with other bacteria to better persist in the host. Virulence factors associated with anaerobes typically confer the abil ity to evade host defenses, adhere to cell surfaces, produce toxins and/ or enzymes, or display surface structures such as capsular polysaccha rides and lipopolysaccharides that contribute to pathogenic potential. The ability of an organism to adhere to host tissues is often critical to the establishment of infection. Some oral species adhere to the epithe lium in the oral cavity. P. gingivalis, a common isolate in periodontal disease, has fimbriae that facilitate attachment. In supragingival plaque, many oral anaerobes are able to attach directly to aerobic bacteria (e.g., Streptococcus species) that are adherent to the tooth's surface. F. nuclea tum is a notable example of these secondary colonizers: it expresses receptors to which almost all oral bacteria can bind and serves as an important bridge between the primary colonizers and subsequent lay ers of bacteria. B. fragilis synthesizes pili, fimbriae, and hemagglutinins that aid in attachment to host cell surfaces in the intestine. Anaerobic bacteria produce several exoproteins that can enhance the organisms' virulence. P. gingivalis produces a collagenase that enhances tissue destruction. Exotoxins produced by clostridial species, including botulinum toxins, tetanus toxin, C. difficile toxins A and B, and five toxins produced by Clostridium perfringens, are among the most virulent bacterial toxins in mouse lethality assays. Anaerobic gram-negative bacteria, such as B. fragilis, P. gingivalis, and Prevotella intermedia, possess lipid A molecules (endotoxins) that are 100–1000 times less biologically potent than endotoxins associated with aero bic gram-negative bacteria; these differences relate to variations in acylation status, length of fatty acids, and number of phosphate groups. This relative biologic inactivity may account for the lower frequency of disseminated intravascular coagulation and purpura in anaerobic gram-negative bacteremia than in facultative and aerobic gramnegative bacillary bacteremia. An exception is the lipopolysaccharide from Fusobacterium, which may account for the severity of Lemierre's syndrome (see "Complications of Anaerobic Head and Neck Infec tions," below). The most extensively studied virulence factor of the nonsporulating anaerobes is the capsular polysaccharide complex of B. fragilis. This organism is unique among anaerobes in its potential for virulence dur ing growth at normally sterile sites. Although it constitutes only 0.5–1% of the normal colonic microbiota, B. fragilis is the anaerobe most com monly isolated from intraabdominal infections and bacteremia. In an animal model of

intraabdominal sepsis, the capsular polysaccharide was identified as the major virulence factor of B. fragilis; this polymer plays a specific, central role in the induction of abscesses. A series of detailed biologic and molecular studies of this virulence factor showed that B. fragilis produces at least eight distinct capsular polysaccharides, far more than the number reported for any other encapsulated bac terium. B. fragilis can exhibit distinct surface polysaccharides either alone or in combination by regulating the expression of these differ ent capsules in an on–off manner through a reversible inversion of DNA segments within the promoters for operons containing the genes required for polysaccharide synthesis. Structural analysis of two of these polysaccharides, PSA and polysaccharide B (PSB), revealed that each polymer consists of repeating units with positively charged free amino groups and negatively charged groups. This structural feature is

rare among bacterial polysaccharides, and the ability of PSA—and, to a lesser extent, PSB—to induce abscesses in animals depends on this zwitterionic charge motif. Intraabdominal abscess induction is related to the capacity of PSA to stimulate macrophages to release cytokines and chemokines—in particular, interleukin (IL) 8, IL-17, and tumor necrosis factor α (TNF-α)—from resident peritoneal cells through a Toll-like receptor 2–dependent mechanism. The release of cytokines and chemokines results in the chemotaxis of polymorphonuclear neu trophils (PMNs) into the peritoneum, where they adhere to mesothelial cells induced by TNF-α to upregulate their expression of intercellular adhesion molecule 1 (ICAM-1). PMNs adherent to ICAM-1-expressing cells probably represent the nidus for an abscess. PSA also activates T cells to produce certain cytokines, including IL-17 and interferon γ, that are necessary for abscess formation.

These virulence factors not only promote persistence of the anaer obe that produces them but also aid in the survival of bystander organ isms and result in bacterial synergies. Clinically, these synergies are evidenced by the fact that anaerobic infections typically involve three to six different organisms. Examples of this synergistic pathogenesis include creation of a favorable environment for growth (e.g., establish ment and maintenance of an anaerobic environment by facultative organisms), inhibition of host defenses (e.g., production of short-chain fatty acids and succinic acid that inhibit the ability of phagocytes to clear facultative organisms), provision of necessary growth factors for other organisms (e.g., oral diphtheroids that produce vitamin K, which is needed by P. melaninogenica), and creation of tissue damage that promotes spread of the infection. In these ways, facultative and obligate anaerobes synergistically potentiate abscess formation. CHAPTER 182 APPROACH TO THE PATIENT Infections Due to Anaerobic Bacteria The physician must consider several points when approaching the patient with a possible infection due to anaerobic bacteria. Infections Due to Mixed Anaerobic Organisms

1. The organisms colonizing mucosal sites are commensals, very few of which typically cause disease. When these organisms do cause disease, it often occurs in proximity to the mucosal site they colonize.
2. For anaerobes to cause tissue infection, they must spread beyond the normal mucosal barriers.
3. Conditions favoring the propagation of anaerobic bacteria, par ticularly a lowered oxidation-reduction potential, are necessary. These conditions exist at sites of trauma, tissue destruction, compromised vascular supply, and necrosis.
4. Frequently, a complex array of infecting microbes can be found, occasionally with >10 different species isolated from a suppura tive site.

5. Anaerobic organisms tend to be found in abscess cavities or in necrotic tissue. The failure of an abscess to yield organisms on routine culture is a clue that the abscess is likely to contain anaerobic bacteria. Often smears of this “sterile pus” are found to be teeming with bacteria when Gram’s stain is applied. Although some facultative organisms (e.g., Staphylococcus aureus) are also capable of causing abscesses, abscesses in organs or deeper body tissues should call anaerobic infection to mind.
6. Gas is found in many anaerobic infections of deep tissues but is not diagnostic because it can be produced by aerobic bacteria as well.
7. Although a putrid-smelling infection site or discharge is con sidered diagnostic for anaerobic infection, this manifestation usually develops late in the course and is present in only 30–50% of cases.
8. Some species (the best example being the B. fragilis group) require specific therapy. However, many synergistic infections can be cured with antibiotics directed at some but not all of the organisms involved. Antibiotic therapy, combined with debride ment and drainage, disrupts the interdependent relationship

among the bacteria, and some species that are resistant to the antibiotic do not survive without the co-infecting organisms. 9. Manifestations of severe sepsis and disseminated intravascu lar coagulation are unusual in patients with purely anaerobic infection. ■ ■EPIDEMIOLOGY Difficulties in the performance of appropriate cultures, contamination of cultures by components of the normal microbiota, and the lack of readily available, reliable culture techniques have made it challenging to obtain accurate data on the incidence or prevalence of anaerobic infections. However, anaerobic infections are encountered frequently, with anaerobes constituting 7–8% and 13–15% of bacteria isolated from inpatients and outpatients, respectively. Bacteremia and soft tissue infections are the most common types of anaerobic infection (Fig. 182-2). Typically, anaerobic bacteria account for <1% of all cases of bacteremia. ■ ■CLINICAL MANIFESTATIONS Although anaerobes can cause infection anywhere in the body, cer tain clinical findings and characteristics are commonly found. These include abscess formation, putrid purulence (due to volatile fatty acid by-products), septic thrombophlebitis, tissue necrosis, and failure to respond clinically to broad-spectrum antibiotics that lack activity against anaerobes. Anaerobic Infections of the Mouth, Head, and Neck Anaero bic bacteria are commonly involved in infections of the mouth, head, and neck (Chap. 37). The predominant isolates are components of the normal microbiota of the upper airways—mainly Prevotella species,

P. asaccharolytica, Fusobacterium species, peptostreptococci, and microaerophilic streptococci. PART 5 Infectious Diseases OROFACIAL INFECTIONS The most common oral infections are odontogenic and include dental caries and periodontal disease (gingi vitis and periodontitis). While dental caries usually manifest with pain, sensitivity, and discoloration of the tooth, periodontal disease involves inflammation of the gums and underlying tissue. In its more severe forms, periodontitis can result in difficulty chewing, loose teeth, and occasionally tooth loss. Severe orofacial infections typically develop as a consequence of dental infection, and the infection can spread from the tooth to different anatomic areas that provide the least resistance, resulting in periapical, periodontal, or pericoronal infections. If the dental surface is completely breached, an endodontic infection (pul pitis) can occur. In late stages of pulpitis, the tooth is generally very sensitive to heat, but cold stimuli may provide relief. Left untreated, pulpitis can progress to invade the alveolar bone and develop into a periapical abscess. The abscesses, particularly those involving

the sec ond and third molars, can occasionally extend into the submandibular, Head and neck Lung Abdomen Soft tissue and joints Bacteremia Catheter-related Surgical site infection FIGURE 182-2 Distribution of types of infection from which anaerobic organisms were cultured at a single hospital over a 7-year period. Head and neck infections included sinusitis, otitis media, and retropharyngeal abscess; abdominal infections included liver abscess, biliary tract infection, bowel obstruction, and intraabdominal abscess; catheter-related infections included those related to peritoneal dialysis catheters and ventriculoperitoneal shunts. (Data from Y Park et al: Clinical features and prognostic factors of anaerobic infections: A 7-year retrospective study. Korean J Intern Med 24:13, 2009.)

sublingual, and submental spaces (Ludwig's angina). This infection results in marked local swelling of tissues, with pain, trismus, and supe rior and posterior displacement of the tongue. Submandibular swelling of the neck and obstruction by the tongue can impair swallowing and cause respiratory obstruction. In some cases, tracheotomy is lifesaving. Microbiologically, dental caries begin with the binding of Strep tococcus mutans and Streptococcus sanguis to the tooth surface, with subsequent further colonization by anaerobes. In contrast, periodon titis is typically associated with P. gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, and Treponema denticola. Fusobacterium, Actinomyces, Peptostreptococcus, and Bacteroides spe cies (other than B. fragilis) are the organisms most commonly isolated from periapical abscesses. ACUTE NECROTIZING ULCERATIVE GINGIVITIS Gingivitis may become a necrotizing infection (trench mouth, Vincent's stomatitis). The onset of disease is usually sudden and is associated with painful bleeding gums, foul breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a yellowish-white or gray "pseudomembrane," which is removable with gentle pressure. Patients may become systemically ill, developing fever, malaise, cervical lymphadenopathy, and leukocytosis. The infection can sometimes extend into the pharynx, resulting in an extremely sore throat, foul breath, and tonsillar pillars that are swollen, red, ulcerated, and covered by a pseudomembrane. Prevotella, Treponema, and Fusobacterium species have been implicated. In some cases, acute necrotizing gingivitis can rapidly progress to noma (cancrum oris), a gangrenous infection that destroys the soft and hard tissues related to the oral cavity. Noma occurs most frequently in young children (1–4 years of age) who have immune dysfunction related to malnutrition and endemic infections (particularly measles). This infection occurs worldwide but is most common in sub-Saharan Africa, where the incidence is 1–7 cases per 1000 children. Although the pathogenesis is not fully understood, infections with F. necrophorum and P. intermedia are thought to be key drivers of this disease. Without treatment, the mortality rate is 70–90%. PERIPHARYNGEAL SPACE INFECTIONS These infections arise from the spread of organisms from the upper airways to potential spaces formed by the fascial planes of the head and neck. The etiology is typically polymicrobial and represents the normal microbiota of the mucosa of the originating site. Peritonsillar abscess (quinsy) is the most common peripharyngeal infection and occurs as a complication of acute tonsillitis. Consistent with its association with tonsillitis, adolescents are most commonly affected. Patients present with a sore throat, dysphagia, peritonsillar swelling, muffled voice, and uvular deviation to the contralateral side. The abscess material typically grows group A Streptococcus in conjunc tion with obligate anaerobes (e.g., Bacteroides, Prevotella, and Pepto streptococcus species) (Chap. 37). Retropharyngeal abscesses typically occur in children 2–4 years of age, although they can occur at any age. Although a suppurative infection of the retropharyngeal lymph nodes is the usual precursor to these abscesses in children, foreign-body ingestion and/or local trauma is more commonly the inciting factor in adults. The clinical presentation shares many features with

peritonsil lar abscesses, but difficulty extending the neck and torticollis are more common with retropharyngeal abscesses. The etiologic agents are the same as in peritonsillar abscesses, with additional aerobic organisms (e.g., S. aureus, viridans streptococci) also playing a role. SINUSITIS AND OTITIS Anaerobic bacteria have been implicated in chronic sinusitis but play little role in acute sinusitis. Numerous studies related to the microbiology of chronic sinusitis have been con ducted; on average, anaerobic bacteria have been found in two-thirds of patients, with many studies demonstrating their presence in >90% of patients. Anaerobic bacteria represent ~40% of all bacteria cultured, with Peptostreptococcus, Prevotella, and Porphyromonas species the most commonly isolated anaerobes. S. aureus and Enterobacteriaceae are the aerobes most commonly recovered in chronic sinusitis. Anaero bic bacteria have been isolated in ~60% of cases of chronic suppurative otitis media in children, but they are not involved in acute otitis media.

COMPLICATIONS OF ANAEROBIC HEAD AND NECK INFECTIONS Direct extension of these infections into contiguous areas can result in addi tional disease manifestations. Cranial spread of these infections can result in osteomyelitis of the skull or mandible or in intracranial infec tions, such as brain abscess and subdural empyema. Caudal spread can produce mediastinitis or pleuropulmonary infection. Hematogenous complications can also result from anaerobic infections of the head and neck. Bacteremia, which occasionally is polymicrobial, can lead to endocarditis or other distant infections. Lemierre’s syndrome (Chap. 37), which is usually due to F. necrophorum, is an acute oro pharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent septic emboli, most commonly to the lung. This infection typically begins with pharyngitis, which is fol lowed by local invasion in the lateral pharyngeal space, with resultant internal jugular vein thrombophlebitis. Central Nervous System (CNS) Infections CNS infections associated with anaerobic bacteria are brain abscess, epidural abscess, and subdural empyema, in which anaerobes are recovered in up to 30, 20, and 10% of cases, respectively. The frequency with which anaerobes are recovered depends in large part on the underlying reason for the infection. For example, brain abscesses are typically due to hematog enous seeding, contiguous spread, penetrating head trauma, or recent surgical intervention. Anaerobic bacteria are most commonly associ ated with brain abscesses resulting from contiguous spread (related to otogenic, odontogenic, and sinus infections), and the pathogens recovered are the same as in these antecedent infections. Facultative or microaerophilic streptococci and coliforms are often part of a mixed infecting flora in brain abscesses. The location of the abscess may also provide insight into the pathogens. Abscesses in the frontal lobe (often associated with sinusitis) are due to anaerobes, streptococci, and staphylococci; temporal lobe and cerebellar abscesses are often related to the oral microbiota and middle-ear pathogens. Obligate anaerobes rarely cause meningitis. Only one obligate anaerobe was identified in a seminal study of 188 bacterial meningitis isolates, and a U.S. national surveillance study of 18,642 such isolates collected between 1977 and 1981 found only five obligate anaerobes. This low incidence may be due, in part, to the fact that many clinical microbiology laboratories do not routinely culture cerebrospinal fluid (CSF) for anaerobes. Pleuropulmonary Infections The lungs are constantly seeded with organisms from the oral microbiota via subclinical microaspira tion that normally occurs in all people. Even though the lung is the site of oxygen exchange and is therefore an overwhelmingly aerobic envi ronment, the organisms most abundant in the lower respiratory tract (as assessed by culture-independent methods) include anaerobes such as Prevotella and Veillonella species, with oral microaerophilic strep tococcal species (e.g., the Streptococcus milleri group) also present in significant abundances. In patients who have impaired bacterial clear ance (due to decreased cough,

dysfunctional mucociliary transport, or alcohol intoxication) and/or increased rates of aspiration (due to neu rologic disorders, impaired consciousness, or swallowing dysfunction), these anaerobic bacteria can establish an infection and result in aspira tion pneumonia, lung abscess, or empyema. These anaerobic infections have an indolent course that may serve as a clinical clue differentiating them from conditions with other etiologies (e.g., chemical pneumoni tis, pneumococcal pneumonia) that often present more acutely. ASPIRATION PNEUMONIA Bacterial aspiration pneumonia must be distinguished from two other clinical syndromes associated with aspiration that are not of bacterial etiology. One syndrome results from aspiration of food or, rarely, other foreign bodies. Obstruction of major airways typically results in difficulty breathing, atelectasis, and moderate nonspecific inflammation. Therapy consists of removal of the foreign body. The second aspiration syndrome relates to chemical pneumonitis caused by inhalation or aspiration of alveolar irritants. Perhaps the most common cause of chemical pneumonitis is Mendelson syndrome, which results from regurgitation and aspira tion of acidic gastric juices. Pulmonary inflammation—including the

destruction of the alveolar lining, with transudation of fluid into the alveolar space—occurs with remarkable rapidity. This syndrome typi cally develops within 4–6 h, often following anesthesia when the gag reflex is depressed. The patient becomes tachypneic, tachycardic, and hypoxic, often in the absence of fever. The leukocyte count may rise, and the chest x-ray may evolve from normal to a complete bilateral “whiteout” within 8–24 h. Sputum production is minimal. The pulmo nary signs and symptoms often resolve quickly with symptom-based therapy, but this condition can culminate in respiratory failure due, in part, to pulmonary edema. Antibiotic therapy is not indicated unless bacterial superinfection occurs.

In contrast to these syndromes, bacterial aspiration pneumonia develops over a period of several days or weeks rather than hours. The pathogenesis includes some combination of an increased bacterial burden, increased virulence of the organisms aspirated, and potential airway damage related to aspiration of gastric fluid. Patients gener ally report fever, malaise, and sputum production. In some patients, weight loss and anemia reflect a more chronic process. Usually the history reveals factors predisposing to aspiration, such as significant alcohol consumption or neurologic impairment due to a previ ous stroke. Severe dental disease is often associated with aspiration pneumonia, but it is not clear whether this association relates to an increased number of oral microbes and/or the presence of organisms with increased virulence. Sputum characteristically is not malodorous unless the process has been ongoing for at least a week. Chest x-rays show consolidation in dependent pulmonary segments: in the basilar segments of the lower lobes if the patient has aspirated while upright and in either the posterior segment of the upper lobe (usually on the right side, given that the right mainstem bronchus has a more vertical orientation) or the superior segment of the lower lobe if the patient has aspirated while supine. CHAPTER 182 A mixed bacterial population with many PMNs is evident on Gram’s staining of sputum. Expectorated sputum is unreliable for anaerobic cultures because of inevitable contamination by the normal oral micro biota. Reliable specimens for culture can be obtained by transtracheal or transthoracic aspiration—techniques that are rarely used at present. Although the culture of protected-brush specimens or bronchoalveolar lavage fluid obtained by bronchoscopy is controversial, more recent data suggest that these approaches can be used without oropharyngeal contamination and can recover anaerobic organisms from the lower respiratory tract in a site-directed manner. Further research is needed to determine how these approaches compare with the previous gold standards. Infections Due to Mixed Anaerobic Organisms ANAEROBIC LUNG ABSCESSES (See also Chap. 132)

These abscesses result from subacute anaerobic pulmonary infection. The clinical presentation typically involves a history of constitutional signs and symptoms (including malaise, weight loss, fever, night sweats, and foul-smelling sputum) that have typically persisted for 1–3 weeks prior to hospitalization. Patients who develop lung abscesses often, but not always, have an antecedent dental infection. Abscess cavities may be single or multiple and generally occur in dependent pulmonary segments (Fig. 182-3). The differential diagnosis for lung abscesses includes pneumonia (including necrotizing pneumonia), a purulent pleural effusion with a bronchopleural fistula, and a pneumatocele. Of note, infection with some aerobic organisms, particularly S. aureus, can develop into a lung abscess without an anaerobic component. Approximately 90% of cases have an anaerobe identified—usually three to six isolates per sample—if careful attention is paid to handling and processing of the abscess sample. The most common isolates include peptostreptococci, Prevotella and Porphyromonas species, and F. nucleatum. An important finding is that ~90% of cultures also demonstrate the presence of aerobic organisms, such as S. aureus, Streptococcus pneumoniae, and Klebsiella pneumoniae. Consistent with the notion that anaerobes are contributing to disease, patients often do not improve clinically until they receive an antibiotic regimen that includes anaerobic coverage. EMPYEMA Empyema is a manifestation of long-standing anaerobic pulmonary infection and manifests with thick, purulent material in

FIGURE 182-3 Chest radiograph (left) and CT image (right) of a lung abscess. The patient aspirated while supine and developed an abscess in the posterior segment of the right upper lobe. Cultures were pretreated and grew only Klebsiella pneumoniae. (Images provided by Gita N. Mody, MD, MPH, Division of Cardiothoracic Surgery, Department of Surgery, The University of North Carolina at Chapel Hill.) PART 5 Infectious Diseases the pleural space, often in association with a bronchopleural fistula. Alternatively, a subdiaphragmatic infection may extend into the pleural space and similarly result in an empyema. The clinical presentation resembles that of other anaerobic pulmonary infections and may include foul-smelling sputum, pleuritic chest pain, and marked chestwall tenderness. This disease process must be differentiated from a parapneumonic effusion resulting from more routine causes of pneu monia (e.g., S. pneumoniae). In the latter instance, the fluid is a thin exu date that has a mean white blood cell (WBC) count of ~5000 cells/mL,

a lactate dehydrogenase level of >200 IU/L, and a pH of ~7.4. In contrast, empyema is characterized by foul-smelling thick pus with a mean WBC count of ~55,000 cells/mL, a lactate dehydrogenase level of >1000 IU/L, and a pH of <7.2 as well as loculations and a thick pleural peel on imaging. Drainage and occasionally decortication of the visceral and parietal pleura are required. Defervescence, a return to a feeling of well-being, and resolution of the process may require several months, particularly in the absence of surgical intervention. Intraabdominal Infections Breach of the gut mucosal surface (e.g., due to trauma, intestinal perforation, or malignancy) allows members of the microbiota to enter the normally sterile perito neum. Accordingly, the offending organisms reflect the microbiota in the affected intestinal region. For example, recovery of Candida species from intraabdominal infections should prompt evaluation of the stomach and proximal small bowel for potential perforation. Furthermore, a study of patients with perforated and gangrenous appendicitis demonstrated that virtually all samples yielded E. coli

and members of the B. fragilis group; peptostreptococci and Bilophila wadsworthia—additional components of the appendiceal and colonic microbiota—also were recovered from >50% of

samples. Notably, some studies have identified an average of 10 different bacterial species, with an anaerobe-to-aerobe ratio of ~3:1. Given that >1000 bacterial species are present in the colonic microbiota, the dominance of such a limited repertoire of bacterial genera and species recovered in intraabdominal infections reflects a combina tion of two factors: the increased propensity of these organisms to result in intraabdominal abscesses and the difficulty faced by clinical microbiology laboratories in culturing the diverse organisms pres ent in these samples. See Chap. 137 for a complete discussion of intraabdominal infections.

Neutropenic enterocolitis (typhlitis) involves marked thickening of the bowel wall (typically >4 mm) in the setting of neutropenia, abdominal pain, and fever. This condition most commonly affects the cecum and may extend to the neighboring terminal ileum and/or proximal colon, but any intestinal region may be involved. Typhlitis generally occurs after 1–2 weeks of chemotherapy-induced neutrope nia associated with treatment of hematologic or, less commonly, solid tumor malignancies, but it can occur regardless of the cause of neutro penia. At least 5% of adults hospitalized for malignancy are thought to develop typhlitis, but this is likely an underestimate. Although the right lower quadrant is the most common location of abdominal pain and tenderness, these symptoms are absent in nearly half of cases; more over, some patients, particularly those taking glucocorticoids, may not experience abdominal pain at all. Given the weakened integrity of the bowel wall and the associated neutropenia, patients often develop bacteremia due to one or more organisms related to the microbiota of the affected intestinal segment. Patients who develop bacteremia due to Clostridium septicum often have relatively severe disease, and identi fication of this organism is highly associated with the presence of malignancy—notably, colon cancer. Medical management including bowel rest, intestinal decompression, and broad-spectrum antibiotic administration is generally successful, although surgical intervention may be required in cases of persistent intestinal bleeding, necrotic bowel, or clinical deterioration suggestive of an ongoing intestinal process. Pelvic Infections Anaerobes are frequently encountered in pel vic inflammatory disease, pelvic abscess, endometritis, tubo-ovarian abscess, septic abortion, and postoperative or postpartum infections. These infections are often of mixed etiology, involving both anaerobes and coliforms; pure anaerobic infections without coliform or other facultative bacterial species occur more often in pelvic than in intraab dominal sites. The major anaerobic pathogens in pelvic abscesses are P. bivia, P. disiens, and the B. fragilis group, but many other anaerobes also have been implicated. See Chap. 141 for a complete discussion of pelvic inflammatory disease. Anaerobic bacteria have been thought to be contributing factors in bacterial vaginosis. This syndrome of unknown etiology is character ized by a profuse malodorous discharge and a change in bacterial ecology that results in replacement of the Lactobacillus-dominated normal microbiota with an overgrowth of anaerobic bacterial species.

Culture-based and culture-independent approaches have identified numerous organisms, including Gardnerella vaginalis, peptostrepto cocci, genital mycoplasmas, and species within the genera Prevotella, Mobiluncus, Atopobium, Leptotrichia, Megasphaera, and Eggerthella. This wide array of implicated bacteria may reflect differences in the overall disease spectrum of bacterial vaginosis and/or a shared physi ologic response to these different organisms. Skin and Soft Tissue Infections Similar to other anatomic sites, skin or soft tissue injured by trauma, ischemia, or surgery creates a suitable environment for anaerobic infections. The infecting bacteria either are introduced directly (e.g., wounds associated with intestinal surgery, decubitus ulcers, or human bites) or originate in contiguous areas (e.g., cutaneous abscesses, rectal abscesses, and axillary sweat gland infections

[hidradenitis suppurativa]). Anaerobes also are often cultured from foot ulcers of diabetic patients. The most common loca tions for anaerobic cellulitis include the neck, trunk, groin (including the genitalia), and legs. The deep soft tissue infections associated with anaerobic bacteria are gas gangrene, synergistic cellulitis (both progres sive and necrotizing), necrotizing fasciitis, and myositis (Chaps. 134 and 159). Gas gangrene (crepitus cellulitis) is most often due to C. perfringens, although other clostridial species have been implicated as well. This infection involves extensive gas formation in the tissue leading to crepitus and a thin, dark, occasionally malodorous discharge. True gas gangrene typically presents with fever and tenderness around the lesion and can rapidly spread; in contrast, there are somewhat more indolent forms of anaerobic cellulitis that may involve some gas formation but often present without fever or extensive local pain and can spread over the course of days rather than minutes. Progressive bacterial synergistic gangrene (Meleney gangrene) is characterized by an area of exquisite pain, redness, and swelling fol lowed by ulceration. As the ulcer enlarges, it is surrounded by a viola ceous ring that fades into a pink edematous border. If it is not promptly treated, the ulcer continues to enlarge, and new, distant ulcers may emerge. Symptoms are limited to pain; fever is not typical. Peptostrep tococci and microaerophilic streptococci are commonly found in the leading edge of the lesions, and S. aureus and Proteus species can be isolated from the ulcerated lesion. Treatment includes surgical removal of necrotic tissue and antimicrobial administration. In contrast, syn ergistic necrotizing cellulitis involves the deep fascia and occurs near the point of bacterial entry. Pain, fever, and systemic symptoms are common. If this form of cellulitis involves the scrotum, perineum, and anterior abdominal wall, it is referred to as Fournier gangrene. S. aureus, the B. fragilis group, Peptostreptococcus species, Clostridium species, Fusobacterium species, and members of the family Enterobacteriaceae are the predominant organisms identified. Necrotizing fasciitis, a rapidly spreading destructive disease of the fascia, is usually attributed to group A streptococci (Chap. 153) but can also be a mixed infection involving anaerobes and aerobes. Polymicro bial necrotizing fasciitis differs from stereotypical group A streptococ cal necrotizing fasciitis in that the initial erythematous, swollen, tender lesions progress over 3–5 days (as opposed to 1–3 days), with conse quent skin breakdown and cutaneous gangrene. Fever, subcutaneous gas, development of anesthesia (often before skin necrosis), and a foulsmelling discharge are common. The particular clinical findings some times suggest the causative agent: regional lymphadenopathy suggests the B. fragilis group; necrosis and gangrene suggest Clostridium species, peptostreptococci, the B. fragilis group, and Enterobacteriaceae; bul lous lesions suggest Enterobacteriaceae; a foul-smelling odor suggests Bacteroides and Clostridium species; and subcutaneous gas suggests peptostreptococci, Clostridium species, and the B. fragilis group. More over, diabetic infections are often associated with Bacteroides species, Enterobacteriaceae, and S. aureus, and infections related to trauma are associated with Clostridium species. Although S. aureus is the typical cause of myositis, anaerobes— particularly C. perfringens—are often recovered from patients with pyogenic myositis. In anaerobic streptococcal myonecrosis, pepto streptococci are often identified along with group A streptococci or

S. aureus. Patients typically present with fever, muscle pain, fatigue, and an elevated creatinine kinase level suggestive of muscle inflammation.

Bone and Joint Infections A comprehensive review of the world literature on anaerobic bone infections through 1975 included >650 cases. Of these, ~400 cases were caused by Actinomyces species; anaero bic cocci and Bacteroides, Fusobacterium, and Clostridium species were most

commonly identified in the remaining cases. Actinomycotic involvement of the jaw was the most common bone infection, with the mandible involved four times as frequently as the maxilla. Patients with cervicofacial actinomycosis (Chap. 180) are often described as having a “lumpy jaw” because of the prominent soft tissue swelling that is sometimes mistaken for malignancy or granulomatous disease. These infections can be chronic in nature, can include the development of sinus tracts, can progress across normal tissue boundaries, and can require prolonged antibiotic treatment to prevent relapse. The verte brae are the second most common location for Actinomyces infection; involvement of the thorax, abdomen, or pelvis is much less frequent. Osteomyelitis involving anaerobes other than Actinomyces species most commonly develops by extension of an adjacent infection (e.g., soft tissue, paranasal sinus, or middle-ear infection). For example, diabetic foot ulcers and decubitus ulcers may be complicated by mixed aerobic–anaerobic osteomyelitis (Chap. 136). Hematogenous seeding of bone by anaerobes is uncommon and is thought to occur in fewer than 10% of cases. The most common sites of anaerobic osteomyelitis are the head (skull and jaw) and the extremities. Fusobacteria have been isolated in pure culture from infections of the mastoid, mandible, and maxilla. Clostridium species have been reported as anaerobic pathogens in cases of osteomyelitis of the long bones following trauma. Anaerobic and microaerophilic cocci are most frequently isolated from infections involving the skull or mastoid; usually, these organisms are present in mixed cultures. CHAPTER 182 In contrast to anaerobic osteomyelitis, anaerobic arthritis (Chap. 135) is uncommon, typically involving a single isolate, and most cases are secondary to hematogenous spread. Although Fusobacterium spe cies accounted for nearly one-third of cases in the preantibiotic era, C. acnes, peptostreptococci, and B. fragilis are now among the more frequent causes of anaerobic septic arthritis. Peptostreptococci and

C. acnes are often found in association with prosthetic joints, Fusobac terium species have a predilection for the sternoclavicular and sacro iliac joints, and clostridial arthritis is especially common after trauma. As a frequent cause of bacteremia, B. fragilis is a common cause of anaerobic septic arthritis; however, arthritis occurs in fewer than 5% of patients with B. fragilis bacteremia. Infections Due to Mixed Anaerobic Organisms Bacteremia B. fragilis is the anaerobe most commonly isolated from blood cultures. Although the frequency of positive cultures appeared to be decreasing in the 1980s, more recent evidence suggests that the rate is now increasing and that the increase may be related to changing demographics, with more patients who are elderly, immunocompro mised, and/or receiving medications that may disrupt the mucosal barrier (e.g., chemotherapy). The source of bacteremia is most often an abscess in the abdomen, female genital tract, or soft tissue. At a large tertiary-care U.S. hospital, 0.8% of all positive blood cultures yielded an anaerobic gram-negative bacillus, with 0.5% yielding B. fragilis. A similar study in France revealed that 0.6% of all positive blood cultures yielded an anaerobic organism; 60% of these isolates were Bacteroides species, and 22% were Clostridium species. Peptostreptococcus and Fusobacterium species are also recovered with significant frequency. Once the organism in the blood has been identified, both the portal of bloodstream entry and the underlying problem that probably led to seeding of the bloodstream can often be deduced from an understand ing of the organism’s normal site of residence. For example, mixed anaerobic bacteremia including B. fragilis usually implies a colonic pathology, with mucosal disruption from neoplasia, diverticulitis, or some other inflammatory lesion. The initial manifestations are determined by the portal of entry and reflect the localized condition. Although the clinical manifestations of B. fragilis bacteremia (e.g., rigors, hectic fevers) are similar to those of aerobic gram-negative

bacillary bacteremia, the incidence of septic shock is lower with B. fra gilis. This difference may be due to differences in the immunostimula tory effects of the different endotoxin structures.

In virtually all cases, isolation of a member of the B. fragilis group from blood indicates underlying infection that is associated with a mortality rate of 60% if untreated. It has been suggested that the mor tality rate depends in part on the species recovered (B. thetaiotaomicron

> P. distasonis > B. fragilis), but it is unclear whether differences in mortality rates relate to intrinsic differences in the virulence of these organisms, in their antimicrobial susceptibility profiles, and/or in the host's immune response. Case–fatality rates appear to increase with the increasing age of the patient (with reported rates of >66% among patients >60 years old), with the isolation of multiple species from the bloodstream, and with the failure to surgically remove a focus of infection. Endocarditis (See also Chap. 133) Although gram-negative anaer obic bacteria only rarely cause endocarditis, their involvement is asso ciated with significant mortality rates (21–43%). Members of the B. fragilis group are the most commonly identified gram-negative anaer obes in endocarditis. Anaerobic streptococci, which are often classified incorrectly, are likely responsible for this disease more frequently than is generally appreciated. Compared with aerobic bacterial endocarditis, endocarditis due to Bacteroides species is less likely to be associated with a history of cardiovascular disease and more likely to involve thromboembolic complications. ■ ■DIAGNOSIS There are three critical steps in the diagnosis of anaerobic infection: (1) proper collection of specimens; (2) rapid transport of the specimens to the microbiology laboratory, preferably in anaerobic transport media; and (3) proper handling of the specimens by the laboratory. Specimens must be collected by meticulous sampling of infected sites, with avoid ance of contamination by the normal microbiota. Samples from sites known to harbor numerous anaerobes (e.g., the mouth, nose, vagina, feces) are not acceptable for anaerobic culture as the presence of the normal microbiota will complicate interpretation of the results in a clinically meaningful manner. In contrast, samples from normally sterile locations (e.g., blood, pleural fluid, peritoneal fluid, CSF, and aspirates or biopsy samples from normally sterile sites) are appropriate for anaerobic culture in clinical microbiology laboratories. As a general rule, liquid or tissue specimens are preferred; if swab specimens must be used, special anaerobic swab systems should be used to help main tain persistence of anaerobes. Liquid samples should be collected in an air-free syringe that is then capped, injected into anaerobic transport bottles, or quickly transported to the clinical microbiology laboratory for immediate culture. PART 5 Infectious Diseases Because of the time and difficulty involved in the isolation of anaer obic bacteria, the diagnosis of anaerobic infections must frequently be based on presumptive evidence. As mentioned previously, anaerobic infections are sometimes suggested by specific clinical factors, such as origins from a site with an anaerobic-rich microbiota (e.g., the intesti nal tract, oropharynx), the presence of an abscess, involvement

> of sites with lowered oxidation-reduction potential (e.g., avascular necrotic tissues), a foul odor, and the presence of gas in tissues. None of these features is necessarily pathognomonic or required for the diagnosis of an anaerobic infection, but these are helpful clues to keep in mind when constructing a differential diagnosis. When cultures of obviously infected sites or purulent material yield no growth, streptococci only, or a single aerobic species (such as E. coli) and Gram's staining reveals a mixed bacterial population, the involvement of anaerobes should be suspected; the implication is that the anaerobic microorganisms have failed to grow because of inadequate transport and/or culture techniques. It is also important to remember that prior antibiotic therapy reduces the cultivability of these bacteria. Failure of an infection to respond to antibiotics that are not active against anaerobes (e.g., aminoglycosides and—in some circumstances—penicillin, cephalosporins, or tetracyclines) suggests an anaerobic etiology.

TREATMENT Anaerobic Infections Similar to successful therapy for other types of infection, treatment for anaerobic infections requires the administration of appropri ate antibiotics, surgical debridement of devitalized tissues, and drainage of any large abscess. Any mucosal breach must be closed promptly to prevent ongoing infection. ANTIBIOTIC THERAPY AND RESISTANCE The antibiotics used to treat anaerobic infections should be active against both aerobic and anaerobic organisms because many of these infections are of mixed etiology. Antibiotic regimens can usu ally be selected empirically on the basis of the location of infection (which provides insight into the likely species involved), the sever ity of infection, and knowledge of local antimicrobial resistance pat terns. Other factors influencing the selection of antibiotics include need for penetration into certain organs (such as the brain) and associated toxicity (Chap. 149). As with all infections, the general maxim is to use the the narrowest-spectrum agent(s) possible so as to minimize the impact on the normal microbiota and the develop ment of resistance. Because of the slow growth rate of many anaerobes, the lack of standardized testing methods and of clinically relevant standards for resistance, and the generally good results obtained with empirical therapy, the role of antibiotic susceptibility testing of these organ isms has been limited in most clinical microbiology laboratories. Instead, isolates are sent to reference laboratories for susceptibility testing when an infection is serious (e.g., brain abscess, meningitis, joint infection), is refractory, or requires prolonged therapy (e.g., osteomyelitis, prosthetic joint infection, endocarditis). Such testing should also be considered when a patient is not responding to anti microbial therapy as expected; multidrug-resistant anaerobes have been reported. Antimicrobial susceptibility testing is also helpful in monitoring the activity of new drugs and recording current resis tance patterns among anaerobic pathogens. The need for susceptibility testing of anaerobic organisms is highlighted by increasing rates of antimicrobial resistance, geo graphic and institutional differences in susceptibility profiles, spe cies-specific antibiograms, and the potential for worse clinical outcomes when ineffective antibiotics are used. These differences preclude making any sweeping generalizations regarding antibiotic therapy for anaerobic infections. For example, rates of resistance to piperacillin-tazobactam have remained low (≤1%) for all Bacteroi des species in the United States, but B. thetaiotaomicron isolates in Korea have a notably higher resistance rate (17%). Clindamycin was historically effective against members of the B. fragilis group, but rates of

resistance have increased to 30–43% in the United States and are >80% in some parts of the world. Furthermore, metronida zole is effective against many different anaerobic organisms and is considered a first-line agent for many anaerobic infections world wide, but, in a population of Colombian patients with refractory periodontitis, 45% of Fusobacterium isolates and 25% of Prevotella and Porphyromonas strains were resistant to metronidazole; this finding underscores the importance of understanding the local antibiogram and of assessing susceptibility profiles in refractory disease. Empirical Therapy Not every anaerobe isolated must be specifically targeted by the antibiotic regimen. Given that infections involving anaerobes are typically polymicrobial, that the cultivation and iden tification of anaerobes are challenging (i.e., not all organisms may be recovered), and that organisms often depend on one another for persistence, clinical resolution of the infection is often achieved with empirical antibiotics targeting the bulk of the organisms recovered. Antibiotics that demonstrate no useful activity against anaerobes include aminoglycosides, monobactams, and trimethoprim-sulfa methoxazole. With the caveat that susceptibility profiles may change with time and geography, the antibiotics that are commonly used

TABLE 182-2 Antimicrobial Therapy That Is Typically Active against Commonly Encountered Anaerobes ANTIBIOTIC(S) CAVEATS Metronidazole This drug is clinically unreliable against

gram-positive non-spore-forming anaerobes (e.g., Actinomyces spp., Propionibacterium spp., Peptostreptococcus spp.). Rates of resistance are increasing in some

gram-negative anaerobes. The newer cephalosporin/β-lactamase combinations have limited anaerobic activity. β-Lactam/β-lactamase inhibitor combinations (ampicillin-sulbactam, ticarcillin–clavulanic acid, piperacillin-tazobactam) Clindamycin Rates of resistance are increasing in Bacteroides spp. Carbapenems (meropenem, imipenem, ertapenem, doripenem) Rates of resistance are currently very low (<5%), although some carbapenemase-producing strains have been identified. Chloramphenicol Some clinical failures have been noted, even

when the isolate is found to be susceptible by in vitro testing. as empirical therapy against anaerobic bacteria include metroni dazole, β-lactam/β-lactamase inhibitor combinations, clindamycin, carbapenems, and chloramphenicol (Table 182-2). Metronidazole is active against gram-negative anaerobes, includ ing nearly all isolates of Bacteroides species, and gram-positive spore-forming organisms, such as C. difficile (Chap. 139) and other Clostridium species. Given intrinsically reduced susceptibility, metronidazole is clinically unreliable against gram-positive non-spore-forming organisms, such as Actinomyces, Propionibacterium, Lactobacillus, Bifidobacterium, Eubacterium, and Peptostreptococ cus. Of note, a few metronidazole-resistant Bacteroides isolates have been identified in the United States, and rates of such resistance have been increasing in Europe. Moreover, the rate of resistance to metronidazole has probably been greatly underestimated in some countries (e.g., the United Kingdom) that use metronida zole susceptibility to discriminate between obligate and facultative anaerobes (with obligate anaerobes defined by their susceptibility). Although the majority of metronidazole-resistant isolates have been identified in patients who have been exposed to the drug, resistant organisms have also been found in metronidazole-naïve patients. More than 90% of clinical isolates from the B. fragilis group produce β-lactamases that are predominantly active against cepha losporins and that are highly active, cell associated, and produced constitutively. Thus, members of the B. fragilis group are presumed to be

resistant to penicillin and ampicillin but may remain suscep tible to extended-spectrum penicillins, particularly in combination with a β-lactamase inhibitor (e.g., ampicillin-sulbactam, piperacillin-

tazobactam). Rates of resistance to ampicillin-sulbactam are increas ing, particularly in P. distasonis, which has a reported resistance rate of 21% in the United States. Because β-lactamase production is not common in Clostridium species, these combination agents are usually effective. Of note, the newer cephalosporin/β-lactamase inhibitors (e.g., ceftolozane-tazobactam, ceftazidime-avibactam) have limited anaerobic activity. Clindamycin is active against many anaerobes. However, rates of resistance to clindamycin among Bacteroides species increased in the United States from 7% in 1981 to 33% in 2010–2012. Resistance to clindamycin among non-Bacteroides gram-negative anaerobes is much less common (<10%). Some Clostridium species are resistant to clindamycin, although C. perfringens typically is not. Carbapenems (ertapenem, doripenem, meropenem, and imipe nem) are active against anaerobes, with fewer than 3% of Bacteroides isolates resistant. There is little difference among resistance rates for specific species, and, of the carbapenems, imipenem typically has the lowest resistance rate. Although the β-lactamase produced by most Bacteroides species is unable to inactivate carbapenems, rare B. fragilis strains have been reported to produce a carbapenemase.

Resistance to chloramphenicol is rare in Bacteroides species. Nationwide surveys in the United States have identified no resistant organisms, but some isolates with elevated minimal inhibitory con centrations (MICs)—i.e., 16 μg/mL—have been noted. Although chloramphenicol has excellent in vitro activity against all clinically relevant anaerobes, some clinical failures have been documented. Therefore, this drug may be less preferable if other active agents are available.

Other antibiotics with more variable activity against anaerobes include the fluoroquinolones and tigecycline. Although many fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin) display reasonable activity against anaerobic organisms other than Bacteroides species, these agents exhibit poor activity against the B. fragilis group. Rates of resistance to moxifloxacin are relatively high (39–83%) among Bacteroides isolates obtained in the United States but are much lower among B. fragilis and B. thetaiotaomicron isolates collected in Korea (8 and 2%, respectively) or Taiwan (8 and 15%, respectively). Tigecycline is active against most anaerobic bacteria, although MICs are somewhat higher for Clostridium species. Tigecycline’s efficacy for treatment of complicated intraabdominal infections is comparable to that of imipenem, and it is therefore recommended as single-agent therapy for these infections. Infections at Specific Sites In clinical situations, specific antibi otic regimens and durations must be tailored to the initial site of infection; the reader is referred to specific chapters on infections at specific sites for recommendations. In general, anaerobic infections are often broadly categorized as originating above or below the dia phragm. This distinction is clinically useful in that the predominant pathogens—and therefore the empirical antibiotic regimens—differ between these two categories of infection. CHAPTER 182 Infections above the diaphragm usually reflect the orodental microbiota, which includes Prevotella, Porphyromonas, Fusobacte rium, and Bacteroides species other than the B. fragilis group along with streptococci (both aerobic and microaerophilic). Accordingly, antibiotic regimens should cover both aerobic and anaerobic bacteria. Given that >70% of these infections include a β-lactamase-producing organism, β-lactam drugs (penicillins and cephalosporins) are poor options as monotherapy. The recommended regimens include clindamycin, a β-lactam/β-lactamase inhibitor combination, or met ronidazole in combination with a drug active against microaerophilic and aerobic streptococci (e.g., penicillin). Infections Due to Mixed Anaerobic Organisms Anaerobic

infections arising below the diaphragm (e.g., colonic and intraabdominal infections) must be treated specifically with agents active against Bacteroides species, including B. fragilis. Single agents suitable for this purpose include cefoxitin, moxi floxacin, a β-lactam/β-lactamase inhibitor combination, or a carbapenem. A two-drug regimen is an alternative, with one drug active against anaerobes and the other against coliforms (e.g., metronidazole with either a cephalosporin or a fluoroquinolone). In addition, if the clinician suspects that gram-positive facultative organisms such as enterococci are involved, therapeutic regimens should include ampicillin or vancomycin. Although clindamycin and cefotetan were previously considered acceptable options for intraabdominal infections involving anaerobes, these drugs are no longer recommended because of escalating rates of resistance in the B. fragilis group. Ampicillin-sulbactam is not recommended because of high rates of resistance among community-acquired strains of E. coli rather than because of resistance in anaerobic bacteria. CNS infections involving anaerobic organisms may be treated with metronidazole, a carbapenem, chloramphenicol, or—if only gram-positive anaerobes are involved—penicillin. Clindamycin and cefoxitin have poor penetration into the CSF and should not be used. Cases of osteomyelitis in which a polymicrobial infection is identified from a bone biopsy specimen should be treated with a regimen that covers both aerobes and anaerobes, as some organisms that are often regarded as a contaminant (e.g., C. acnes) may have a pathogenic role. When an anaerobic organism is recognized as a

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