Anaerobic Infections in Children

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Abstract Anaerobic bacteria commonly cause infection in children. Anaerobes are the most predominant components of the normal human skin and mucous membranes bacterial flora and are therefore a common cause of bacterial infections of endogenous origin. Because of their fastidious nature, they are difficult to isolate from infectious sites and are often overlooked. Anaerobic infections can occur in all body sites, including the central nervous system, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft tissues. They colonize the newborn after delivery and have been recovered from several types of neonatal infections. These include cellulitis of the site of fetal monitoring, neonatal aspiration pneumonia, bacteremia, conjunctivitis, omphalitis, and infant botulism. The failure to direct adequate therapy against these organisms may lead to clinical failures. Their isolation requires appropriate methods of collection, transportation, and cultivation of specimens. Treatment of anaerobic infection is complicated by the slow growth of these organisms, by their polymicrobial nature, and by the growing resistance of anaerobic bacteria to antimicrobials. Antimicrobial therapy is often the only form of therapy required, whereas in others it is an important adjunct to a surgical approach. Because anaerobic bacteria generally are recovered mixed with aerobic organisms, the choice of appropriate antimicrobial agents should provide for adequate coverage of both types of pathogen.

1 Introduction

Infections due to anaerobic bacteria are common in children and may be serious and life threatening. The recent increased recovery of these organisms from children has led to greater appreciation of the role anaerobes play in pediatric infections. Anaerobic infections can occur in all body sites, including the central nervous system, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft

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tissues. Anaerobes colonize the newborn after delivery and have been recovered from several types of neonatal infections. These include cellulitis of the site of fetal monitoring, neonatal aspiration pneumonia, bacteremia, conjunctivitis, omphalitis, and infant botulism.

Anaerobes are the predominant components of the normal human skin and mucous membranes bacterial flora [1, 2] and are therefore a common cause of bacterial infections of endogenous origin. Because of their fastidious nature, these organisms are difficult to isolate from infectious sites and are often overlooked. Their exact frequency is difficult to ascertain because of the inconsistent use of adequate methods for their isolation and identification. The failure to direct adequate therapy against these organisms may lead to clinical failures. Their isolation requires appropriate methods of collection, transportation, and cultivation of specimens [3–5]. Treatment of anaerobic infection is complicated by the slow growth of these organisms, by their polymicrobial nature, and by the growing resistance of anaerobic bacteria to antimicrobials.

2 Microbiology

The clinically important anaerobic bacteria are six genera of Gram-negative rods (*Bacteroides, Prevotella, Porphyromonas, Fusobacterium, Bilophila*, and *Sutterella*), Gram-positive cocci (primarily *Peptostreptococcus*), Gram-positive spore-forming (*Clostridium*) and non-spore-forming bacilli (*Actinomyces, Propionibacterium, Eubacterium, Lactobacillus*, and *Bifidobacterium*), and Gram-negative cocci (mainly *Veillonella*) (Table 1) [5, 6]. The frequency of recovery of anaerobic strains differs in various infectious sites (Table 2). Mixed infections caused by numerous aerobic and anaerobic organisms are observed commonly in clinical situations [3, 4].

The taxonomy of anaerobic bacteria has changed in recent years because of their improved characterization using genetic studies [5, 7]. The ability to differentiate between similar strains enables better characterization of type of infection and predicted antimicrobial susceptibility. The frequency of recovery of anaerobic strains differs in various infectious sites.

2.1 Gram-Positive Spore-Forming Bacilli

Anaerobic spore-forming bacilli belong to the genus *Clostridium*. The clostridia found most frequently in clinical infections are *Clostridium perfringens, Clostridium septicum, Clostridium ramosum, Clostridium novyi, Clostridium sordellii, Clostridium histolyticum, Clostridium fallax, Clostridium bifermentans*, and *Clostridium innocuum*.

C. perfringens, the most commonly recovered clostridial isolate, is an inhabitant of soil and of intestinal contents of humans and animals and is the most

Table 1 Classification of predominant recovered anaerobic bacteria

Gram-positive cocci
Peptostreptococcus spp., *P. magnus, P. asaccharolyticus, P. prevotii, P. intermedius, P. anaerobius, P. micros*
Microaerophilic streptococci (not true anaerobes)
Gram-positive (non-spore-forming) bacilli
P. acnes
Propionibacterium propionicum
Eubacterium lentum
Bifidobacterium eriksonii
Bifidobacterium dentium
Actinomyces species: *A. isrealii, A. naeslundii, A. viscosus, A. odontolyticus, A. meyerii*
Arachnia propionica
Gram-positive (spore-forming) bacilli
Clostridium species: *C. perfringens, C. ramosum, C. septicum, C. novyi, C. histolytica, C. sporogenes, C. difficile, C. bifermentans, C. butyricum, C. innocuum, C. sordellii, C. botulinum, C. tetani*
Gram-negative bacilli
Bacteroides fragilis group: *B. fragilis, B. thetaiotaomicron, B. distasonis, B. vulgatus, B. ovatus, B. uniformis*
Other *Bacteroides*: *B. gracilis, B. ureolyticus*
Pigmented *Prevotella* spp. *P. melaninogenica, P. intermedia, P. denticola, P. loescheii, P. corporis, P. nigrescens*
Other *Prevotella* spp.: *P. oris, P. buccae, P. oralis* group, (*P. oralis, P. buccalis, P. veroralis*), *P. bivia, P. disiens*
Porphyromonas spp: *P. asaccharolytica, P. gingivalis, P. endodontalis*
Fusobacterium species: *F. nucleatum, F. necrophorum, F. gonidiaformans, F. naviforme, F. mortiferum, F. varium*

frequently encountered histotoxic clostridial species and elaborates a number of necrotizing extracellular toxins [8] and can cause a devastating illness with high mortality. Clostridial bacteremia is associated with extensive tissue necrosis, hemolytic anemia, and renal failure.

Recovery of *C. septicum* has been often found associated with malignancy. *Clostridium botulinum* (types A and B) is usually associated with food poisoning and rarely with wound infections. Infant botulism occurs with types A, B, and F [8]. Disease caused by *C. botulinum* usually is an intoxication produced by ingestion of contaminated food (uncooked meat, poorly processed fish, and improperly canned vegetables), containing a highly potent neurotoxin [9]. The polypeptide neurotoxin is relatively heat labile, and food containing this toxin may be rendered innocuous by exposure to 100°C for 10 min.

Clostridium difficile has been incriminated as the causative agent of antibiotic-associated and spontaneous diarrhea and colitis [10]. *Clostridium tetani* is found in soil and rarely is isolated from human feces. Infections caused by this bacillus are a result of soil contamination of wounds with *C. tetani* spores [9] that germinate and produce neurotoxin.

Table 2 Anaerobic bacteria most frequently encountered in clinical specimens

Organism	Infectious site
Gram-positive cocci	
Peptostreptococcus sp.	Respiratory tract, intraabdominal, and soft tissue infections
Microaerophilic streptococci[a]	Sinusitis, brain abscesses
Gram-positive (non-spore-forming) bacilli	
Actinomyces sp.	Intracranial abscesses, chronic mastoiditis, aspiration pneumonia, head and neck infections
P. acnes	Shunt infections (cardiac, intracranial), infections associated with foreign body
Bifidobacterium sp.	Chronic otitis media, cervical lymphadenitis, abdominal infections
Gram-positive (spore-forming) bacilli	
Clostridium sp.	
C. perfringens	Soft tissue infection, sepsis, food poisoning
C. septicum	Sepsis, neutropenic enterocolitis
C. difficile	Colitis, antibiotic-associated diarrheal disease
C. botulinum	Botulism
C. tetani	Tetanus
C. ramosum	Soft tissue infections
Gram-negative bacilli	
B. fragilis group (*B. fragilis*, *B. thetaiotamicron*)	Intraabdominal and female genital tract infections, sepsis, neonatal infections
Pigmented *Prevotella* and *Porphyromonas*	Orofacial infections, aspiration pneumonia, periodontitis
P. oralis	Orofacial infections
P. oris-buccae	Orofacial infections, intraabdominal infections
B. bivius, B. disiens	Female genital tract infections
Fusobacterium sp.	
F. nucleatum	Orofacial and respiratory tract infections, brain abscesses, bacteremia
F. necrophorum	Aspiration pneumonia, bacteremia

[a]Not obligate anaerobes.

2.2 Gram-Positive Non-Spore-Forming Bacilli

Anaerobic, Gram-positive, non-spore-forming rods comprise part of the microflora of the gingival crevices, the gastrointestinal tract, the vagina, and the skin. Several distinct genera are recognized: *Actinomyces, Arachnia, Bifidobacterium, Propionibacterium, Eubacterium,* and *Lactobacillus*.

Actinomyces israelii and *Actinomyces naeslundii* have been recovered from intracranial abscesses, chronic mastoiditis, aspiration pneumonia, and peritonitis [4, 6]. Actinomycosis occurs most commonly in the tissues of the face and neck, lungs, pleura, and ileocecal regions. Bone, pericardial, and anorectal lesions are less common, but virtually any tissue may be invaded; a disseminated, bacteremic form has been described.

Propionibacterium ordinarily is not a pathogen but can be found in association with implanted cardiac or neurogenic shunt prostheses [11] or as a cause of endocarditis on previously damaged valves. *Propionibacterium acnes* and *Propionibacterium granulosum*, the two most common species, may be isolated from blood cultures but are associated only rarely with bacteremia or endocarditis. Because they are part of the normal skin flora, they are common laboratory contaminants. *P. acnes* may play a role in the pathogenesis of acne vulgaris.

2.3 Gram-Negative Bacilli

Bacteroides spp. The species of Bacteroidaceae that occur with greatest frequency in clinical specimens belong to the *B. fragilis* group. These organisms are resistant to penicillins mostly through the production of beta-lactamase. The group includes *B. fragilis* (the most commonly recovered member), *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, and *Bacteroides vulgatus*. They are part of the normal gastrointestinal flora [2] and predominate in intra-abdominal infections and infections that originate from that flora (i.e., perirectal abscesses and decubitus ulcers) [4, 6].

Pigmented *Prevotella* (*Prevotella melaninogenica* and *Prevotella intermedia*) and *Porphyromonas* (*Porphyromonas asaccharolytica*) and non-pigmented *Prevotella* (*Prevotella oralis*, *Prevotella oris*) are part of the normal oral and vaginal flora and the predominant Gram-negative anaerobic species isolated from respiratory infections and their complications. These include aspiration pneumonia, lung abscess, chronic otitis media, chronic sinusitis, abscesses around the oral cavity, human bites, paronychia, brain abscesses, and osteomyelitis [12]. *Prevotella bivia* and *Prevotella disiens* are important isolates in obstetrical and gynecological infections.

Fusobacterium species seen most often in clinical infections are *Fusobacterium nucleatum, Fusobacterium necrophorum, Fusobacterium mortiferum,* and *Fusobacterium varium*. *F. nucleatum* is the predominant *Fusobacterium* from clinical specimens, often associated with oral, pulmonary, and intracranial infections [13]. They are often isolated from abscesses, obstetrical and gynecological infections, blood, and wounds.

The growing resistance of Gram-negative anaerobic bacilli to penicillins has been noticed in the last decade [14]. These include the pigmented *Prevotella* and *Porphyromonas, Fusobacterium* spp., *P. oralis, B. disiens*, and *B. bivius*. The main mechanism of resistance is through the production of the enzyme beta-lactamase. Complete identification and susceptibility testing and ability to produce beta-lactamase by members of the *B. fragilis* group as well as other Gram-negative anaerobic bacilli are factors of practical importance when making choices between antimicrobials for the therapy of pediatric infections involving these organisms.

The recovery rate of the different anaerobic Gram-negative bacilli in infected sites is similar to their distribution in the normal flora [4, 6]. *B. fragilis* group was more often isolated in sites proximal to the gastrointestinal tract (abdomen, bile),

pigmented *Prevotella* spp. were more prevalent in infections proximal to the oral cavity (bones, sinuses, chest), and *P. bivius* and *P. disiens* were more often isolated in obstetric and gynecologic infections. Knowledge of this common mode of distribution allows for logical empiric choice of antimicrobials adequate for the therapy of infections in these sites.

2.4 Gram-Positive Cocci

The species most commonly isolated are *Peptostreptococcus magnus*, *Peptostreptococcus asaccharolyticus*, *Peptostreptococcus anaerobius*, *Peptostreptococcus prevotii*, and *Peptostreptococcus micros*. These organisms are part of the normal flora of the mouth, upper respiratory tract, intestinal tract, vagina, and skin.

These organisms are also predominant isolates in all types of respiratory infections, including chronic sinusitis, mastoiditis, acute and chronic otitis media, aspiration pneumonia, lung abscess, necrotizing and subcutaneous and soft tissue infections [15]. They generally are recovered mixed with other aerobic or anaerobic organisms, but in many cases they are the only pathogens recovered. This may be of particular significance in cases of bacteremia or acute otitis media. Microaerophilic streptococci are of particular importance in chronic sinusitis and brain abscesses [16].

2.5 Gram-Negative Cocci

There are three species described as anaerobic Gram-negative cocci: *Veillonella, Acidaminococcus*, and *Megasphaera*. There are two described species of *Veillonella* and only one each of the other two genera. The veillonellae are the most frequently involved of the three species and are part of the normal flora of the mouth, vagina, and the small intestine of some persons. Although they rarely are isolated from clinical infections, these organisms have been recovered occasionally from almost every type of anaerobic infection [17].

3 Pathogenicity and Virulence

3.1 Anaerobes as Normal Flora

The human body mucosal and epithelial surfaces are colonized with aerobic and anaerobic microorganisms [1, 2]. The organisms at the different sites tend to belong to certain major bacterial species and their presence in that location is predictable. The relative and total counts of organisms can be affected by various factors, such as age, diet, anatomic variations, illness, hospitalization, and antimicrobial therapy. However, the predictable pattern of bacterial flora remains stable through life, despite their subjection to perturbing factors. Anaerobes outnumber aerobic

Table 3 Normal flora

Site	Number of organisms/gram		Predominant anaerobic bacteria
	Aerobes	Anaerobes	
Skin			*P. acnes* *Peptostreptococcus* sp.
Mouth/upper respiratory tract	$10^{8–9}$	$10^{9–11}$	Pigment *Prevotella* and *Porphyromonas* spp. *Fusobacterium* spp. *Peptostreptococcus* spp. *Actinomyces* spp.
Gastrointestinal tract			
Upper	$10^{2–5}$	$10^{3–7}$	*B. fragilis* group *Clostridium* spp.
Lower	$10^{5–9}$	$10^{10–12}$	*Peptostreptococcus* spp. *Bifidobacterium* spp. *Eubacterium* spp.
Female genital tract	10^{8}	10^{9}	*Peptostreptococcus* spp. *P. bivia* *P. disiens*

bacteria in all mucosal surfaces, and certain organisms predominate in the different sites (Table 3).

Knowledge of the composition of the flora at certain sites is useful for predicting which organisms may be involved in an infection adjacent to that site and can assist in the selection of a logical antimicrobial therapy, even before the exact microbial etiology of the infection is known.

The anaerobic microflora of the total body skin is largely made up of the genus *Propionibacterium* [11] and to a lesser extent *Peptostreptococcus* spp. The perineum and lower extremity may harbor members of the colonic and vaginal flora. The microflora of the upper airways including oral cavity, nasopharynx, and oropharynx is complex and contains many kinds of obligate anaerobes. The ratio of anaerobic bacteria to aerobic bacteria in saliva is approximately 10:1. The total count of anaerobic bacteria in the saliva and elsewhere in the oral cavity reaches 10^{7}–10^{8}/mL.

The gastrointestinal flora varies in bacterial concentration at different levels. The stomach acidity accounts for the reduction in the number of organisms that are swallowed from the oropharynx. The stomach, duodenum, jejunum, and proximal ileum normally contain relatively few bacteria. However, the flora becomes more complex, and the number of different bacterial species increases in the distal portion of the gastrointestinal tract. However, interruption in intestinal motility may result in an increase in the number of anaerobic and aerobic bacteria. The bacterial counts in the small intestine are relatively low, with total counts of 10^{2}–10^{5} organisms/mL. The organisms that predominate up to the ileocecal valve are Gram-positive facultative, while below that structure *Bacteroides* organisms (mostly *B. fragilis*, *Peptostreptococcus*, and *Clostridium* spp.) and coliform bacteria are the major isolates [2]. The mean number of bacteria in the colon is approximately 10^{12}

bacteria/g fecal material. Approximately 99.9% of these bacteria are anaerobic (ratio of aerobes to anaerobes is 1 to 1,000–10,000). In the colon 300–400 different species or types of bacteria can be found.

The female genital flora comprises a mixture of aerobic and anaerobic flora. However, the concentration and type of bacteria is less stable than that of the gastrointestinal flora and can be influenced by antibiotic therapy, pregnancy, and gynecologic surgery. A concentration of 10^8/mL organisms is found in the reproductive years. Changes occur in the number of organisms at the various stages of the menstrual cycle [18, 19]. The predominant aerobic organisms are *Lactobacillus*, and the predominant anaerobic bacteria are *Lactobacillus, Peptostreptococcus, Prevotella*, and *Bacteroides* spp. Bacterial vaginosis is associated with an increase in the number of anaerobic flora and a decrease in the concentration of lactobacilli [19].

Most infections due to anaerobic bacteria originate from the endogenous mucosal membrane and skin flora. Anaerobes belonging to the indigenous flora of the oral cavity can be recovered from various infections adjacent to that area, such as cervical lymphadenitis; subcutaneous abscesses and burns in proximity to the oral cavity; human and animal bites; paronychia; tonsillar and retropharyngeal abscesses; chronic sinusitis; chronic otitis media; periodontal abscess; thyroiditis; aspiration pneumonia; and bacteremia associated with one of the above infections [4, 6]. The predominant anaerobes recovered in these infections are *Prevotella* and *Porphyromonas,* and *B. oralis*, *Fusobacterium*, and *Peptostreptococcus* spp. which are all part of the normal flora of the mucous surfaces of the oropharynx (Table 4).

A similar correlation exists in infections associated with the gastrointestinal tract. Such infections include peritonitis following rupture of appendix, liver abscess, abscess and wounds near the anus, intraabdominal abscess, and bacteremia associated with any of these infections [4, 6]. The anaerobes that predominate in these infections are *B. fragilis* group, clostridia, and *Peptostreptococcus* spp.

Another site with a correlation between the normal flora and the anaerobic bacteria recovered from infected sites is the genitourinary tract. The infections involved are amnionitis, septic abortion, and other pelvic inflammations [4, 6]. The anaerobes usually recovered from these sites are species of anaerobic Gram-negative bacteria and *Peptostreptococcus* spp. Organisms belonging to the vaginal–cervical flora are also important pathogens of neonatal infections. They can be acquired by the newborn prior to delivery in the presence of amnionitis, or during passage through the birth canal.

3.2 Conditions Predisposing to Anaerobic Infection

The clinical situations that predispose to anaerobic infections include exposure of the sterile body sites to high inoculum of indigenous mucous membrane flora. Poor blood supply and tissue necrosis lower the oxidation–reduction potential and favor the growth of anaerobic bacteria. Any condition that lowers the blood supply to an affected area of the body can predispose to anaerobic infection. Therefore, trauma,

Table 4 Recovery of anaerobic bacteria in infectious sites

Infection	*Peptostreptococcus* sp.	*Clostridium* sp.	*B. fragilis* group	*Pigmented Prevotella* and *Porphyromonas*	*P. bivius* *P. disien*	*Fusobacterium* sp.
Bacteremia	1	1	2	1	0	1
Central nervous system	2	1	1	2	0	1
Head and neck	3	1	1	3	0	3
Thoracic	2	1	1	3	0	3
Abdominal	3	3	3	1	1	1
Obstetric-gynecology	3	2	1	1	2	1
Skin and soft tissue	2	1	2	2	1	1

Frequency of recovery in anaerobic infections: 0, none; 1, rare (1–33%); 2, common (34–66%); 3, very common (67–100%).

foreign body, malignancy, surgery, edema, shock, colitis, and vascular disease may predispose to anaerobic infection. Previous infection with aerobic or facultative organisms also may make the local tissue conditions more favorable for the growth of anaerobic bacteria. The human defense mechanisms also may be impaired by anaerobic conditions and anaerobic bacteria.

Suppuration, abscess formation, thrombophlebitis, and gangrenous destruction of tissue associated with gas formation are the hallmark of anaerobic infection. Anaerobes are especially common in chronic infections, and they are commonly seen after therapy with antimicrobials that fail to eradicate them (i.e., aminoglycosides, trimethoprim-sulfamethoxazole, and the older quinolones).

Certain infections are very likely to involve anaerobes as important pathogens and their presence should always be assumed. Such infections include brain abscess, oral or dental infections, human or animal bites, aspiration pneumonia and lung abscesses, peritonitis following perforation of viscus, amnionitis, endometritis, septic abortions, tubo-ovarian abscess, abscesses in and around the oral and rectal areas, and pus-forming necrotizing infections of soft tissue, muscle, and tumors.

3.3 Virulence Factors

Anaerobes contribute to the severity of infection through their synergy with their aerobic counterpart and with each other [20]. Anaerobic bacteria require more time than aerobic bacteria to become virulent. This is because some of the major virulence factors of certain anaerobes (i.e. the production of a capsule by *Bacteroides*) are expressed only after the infection has become chronic [21].

Anaerobes possess several important virulence factors, including the presence of surface structures such as capsule polysaccharide or lipopolysaccharide, production of superoxide dismutase and catalase, immunoglobulin proteases, coagulation promoting and spreading factors (such as hyaluronidase, collagenase, and fibrinolysin), and adherence factors [22]. Other factors that enhance the virulence of anaerobes include mucosal damage, oxidation–reduction potential drop, and the presence of hemoglobin or blood in an infected site.

An indirect pathogenic role of some anaerobes is their ability to produce the enzyme beta-lactamase. Beta-lactamase-producing bacteria can be involved directly in the infection and protect not only themselves but also other penicillin-susceptible organisms from the activity of penicillins. This can occur when the enzyme is secreted into the infected tissue or abscess fluid in sufficient quantities to degrade the beta-lactam ring of penicillin or cephalosporin before it can kill the susceptible bacteria [23].

4 Diagnostic Microbiology

4.1 Collection of Specimens for Anaerobic Bacteria

The proper management of anaerobic infection depends on appropriate documentation of the bacteria causing the infection. Without such an approach, the patient

may be exposed to inappropriate, costly, and undesirable antimicrobial agents with adverse side effects. Certain or all of the anaerobes may not be recovered when the specimen is not promptly placed under anaerobic conditions for transport to the laboratory. If contamination of the specimen with normal flora occurs, anaerobes may be recovered that are not related with the patient's illness.

The essential elements requiring the cooperation of the physician and the microbiology laboratory for appropriate documentation of anaerobic infection are the collection of appropriate specimens, the expeditious transportation, and careful laboratory processing.

Appropriate cultures for anaerobic bacteria are especially important in mixed aerobic and anaerobic infections [5]. Techniques or media that are inadequate for isolation of anaerobic bacteria can lead to the assumption that the aerobic organism(s) recovered are the sole pathogens. This may cause the clinician to direct therapy toward only those aerobic organisms.

Specimens should be obtained free of contamination so that normal flora organisms are excluded. Because indigenous anaerobes often are present on the surfaces of skin and mucous membranes in large numbers, even minimal contamination of a specimen with normal flora can give misleading results. Specimens should therefore be classified as acceptable or unacceptable according to their acceptability for anaerobic culture. Appropriate specimens for anaerobic cultures should be obtained using a technique that bypasses the normal flora. Unacceptable or inappropriate specimens can yield normal flora also and therefore have no diagnostic value.

Acceptable specimens (Table 5) include blood specimens; aspirates of body fluids (pleural, pericardial, cerebrospinal, peritoneal, and joint fluids); urine collected by percutaneous suprapubic bladder aspiration; abscess contents; deep wound aspirates; and specimens collected by special techniques, such as transtracheal aspirates or direct lung puncture. Lower respiratory tract specimens are difficult to obtain without contamination with indigenous flora. Double lumen catheter bronchial

Table 5 Methods for collection of specimen for anaerobic bacteria

Infection site	Methods
Abscess or body cavity	Aspiration by syringe and needle Incised abscesses – syringe or swab (less desirable); specimen obtained during surgery after cleansing the skin
Tissue or bone	Surgical specimen using tissue biopsy or curette
Sinuses or mucus surface abscesses	Aspiration after decontamination or surgical specimen
Ear	Aspiration after decontamination of ear canal and membrane; in perforation: cleanse ear canal and aspirate through perforation
Pulmonary	Transtracheal aspiration, lung puncture, bronchoscopic aspirate[a]
Pleural	Thoracentesis
Urinary tract	Suprapubic bladder aspiration
Female genital tract	Culdocentesis following decontamination, surgical specimen Transabdominal needle aspirate of uterus intrauterine brush[a]

[a]Using double lumen catheter and quantitative culture.

brushing and bronchial lavage, cultured quantitatively, can be useful. Specimens obtained from normally sterile sites may be collected after thorough skin decontamination as is the case for the collection of blood, spinal, joint, or peritoneal fluids.

4.2 Transportation of Specimens

Specimens should be transported to the microbiology laboratory promptly. Various transport devices are available that generate oxygen-free environment using a mixture of carbon dioxide, hydrogen, and nitrogen, that contain an indicator to illustrate aerobic condition. Specimens should be placed into an anaerobic transporter as soon as possible after their collection. Aspirates of liquid specimen or tissue are always preferred to swabs. Liquid specimens may be inoculated into an anaerobic transport vial. A plastic or glass syringe and needle also may be used for transport. After collection, all air should be expelled from the syringe and the needle tip should be inserted into a sterile rubber stopper. No more than 30 min should elapse before the specimen is plated, because air gradually diffuses through the plastic syringe wall.

Swabs or tissue specimens can be transported in an anaerobic jar or in a Petri dish placed in a sealed plastic bag that can be rendered anaerobic by a catalyzer.

4.3 Laboratory Diagnosis

Laboratory diagnosis of anaerobic infections starts with the examination of a Gram-stained smear of the specimen. This can reveal important preliminary information about the types of bacteria present, suggest empiric therapy, and serve as a quality control on the final culture results. The laboratory should be able to isolate all of the morphological types in the approximate ratio in which they are seen.

Detailed procedures of the methods for cultivation of anaerobes can be found in microbiology manuals [5]. Cultures should be placed immediately under anaerobic conditions and incubated for 48 h or longer. An additional period of 36–46 h is generally needed to completely identify the anaerobic bacteria to a species level, using biochemical tests. Kits of these biochemical tests are commercially available. Gas liquid chromatography of metabolites can be employed to assist in the identification of anaerobes. Nucleic acid probes and polymerase chain reaction (PCR) methods are being developed for rapid identification of anaerobic bacteria. Identification of an anaerobe to a species level is often cumbersome, expensive, and time consuming, taking up to 72 h. The decision of what level of speciation is adequate for identifying an anaerobic organism is often controversial.

Occasionally, identification of an organism can provide the diagnosis, as is the case with *C. difficile* in a patient with colitis or *C. botulism* in infants with botulism. Identifying the *B. fragilis* group that is more often causing bacteremia and septic complications has significant prognostic value.

Identification of an anaerobe is also helpful in selecting what antibiotic to use to treat species whose antibiotic susceptibility is predictable. Until the late 1970s, most clinically significant anaerobes except *B. fragilis* group were susceptible to penicillin [14]. Therefore, extensively speciating and antibiotic susceptibility testing were generally unnecessary. In the last decade, however, there is more variability in antimicrobial susceptibility patterns that necessitate more extensive speciation as well as antimicrobial susceptibility testing for some anaerobic bacteria. Organisms that should be identified include isolates from sterile body sites (i.e., blood, cerebrospinal fluid, and joint), those with particular epidemiological or prognostic significance (e.g., *C. difficile*), and organisms with variable of unique susceptibility

4.4 Antimicrobial Susceptibility Testing

The antimicrobial susceptibility of anaerobes has become less predictable over the last decade, as resistance to several antimicrobial agents especially by Gram-negative bacilli has increased. Screening of anaerobic Gram-negative bacilli isolates (particularly *Prevotella*, *Bacteroides*, and *Fusobacterium* species) for production of beta-lactamase may be important. This can provide information about their penicillin susceptibility. However, occasional resistance to beta-lactam antibiotics can occur through other mechanisms.

Routine susceptibility testing of all anaerobic isolates is time consuming and often unnecessary. Susceptibility testing should be limited to organisms isolated from blood cultures, bone, central nervous system, and serious infections when isolated in pure culture from properly collected specimens. Antibiotics tested should include penicillin, a broad-spectrum penicillin, a penicillin plus a beta-lactamase inhibitor, clindamycin, chloramphenicol, a newer quinolone, a second-generation cephalosporin (e.g., cefoxitin), metronidazole, and a carbapenem (e.g., imipenem). The recommended method by the National Committee for Clinical Laboratory Standards (NCCLS) includes agar microbroth and macrobroth dilution [24]. Newer methods include the E-test and the spiral gradient endpoint system.

5 Prevention

The appropriate therapy of acute infections can prevent the development of chronic infections where anaerobes predominate. In settings where anaerobic infections are expected, such as intraabdominal and wound infection following surgery, antimicrobial prophylaxis can reduce the risk of such infection. Prophylactic therapy prior to surgery is given when the surgical site is expected to be contaminated by the normal flora of the mucous membrane at the operated site. Cefazolin is effective in surgical prophylaxis in sites distant from the oral or rectal areas. Cefoxitin is the drug of choice in procedures that involve the oral, rectal, or vulvovaginal areas

because its spectrum extends to both the aerobic and anaerobic flora likely to be encountered.

Prevention and early therapy of conditions that may lead to anaerobic infection can reduce their rate. Aspiration pneumonia and its complication can be prevented by reducing the aspiration of oral flora by improving patient's neurological status, repeated suctioning of oral secretion, improving oral hygiene, and maintaining lower stomach pH. Skin and soft tissue infections can be prevented by irrigation and debridement of wounds and necrotic tissue, drainage of pus, and improvement of blood supply.

6 Clinical Infections

6.1 Central Nervous System Infections

Anaerobic bacteria can cause a variety of intracranial infections. They often induce brain abscess, subdural empyema, and infrequently cause epidural abscess and meningitis. The main source of brain abscess is an adjacent, generally chronic infection in the ears, mastoids, sinuses, oropharynx, teeth, or lungs [25]. Ear or mastoid infection tends to spread to the temporal lobe or cerebellum, while sinusitis often causes abscess of the frontal lobe. Hematogenous spread often occurs after dental, oropharyngeal, or pulmonary infection. Rarely bacteremia of another origin or endocarditis can lead to such infection.

Meningitis is rare and can follow respiratory infection or be a complication of a cerebrospinal fluid shunt. Shunt infections are generally caused by skin flora such as *P. acnes* [11], or in instances of ventriculoperitoneal shunts that perforate the gut by anaerobes of enteric origin (i.e., *B. fragilis*) [26]. *C. perfringens* can cause brain abscesses and meningitis following head injuries or after intracranial surgery [27].

The anaerobic bacteria generally recovered from brain abscesses that complicate respiratory and dental infections include *Prevotella*, *Porphyromonas*, *Bacteroides, Fusobacterium*, and *Peptostreptococcus* spp. Microaerophilic and other streptococci are also often isolated. Actinomyces is less frequently encountered.

Encephalitis often precedes abscess formation, it then progresses to liquification, pus formation, and eventually to fibrous encapsulation [28]. At the stage of encephalitis, antimicrobial therapy accompanied by measures to control the increase in the intracranial pressure and can prevent the abscess formation. Once an abscess has formed, surgical excision or drainage may be needed, combined with a long course of antibiotics (4–8 weeks). Some neurosurgeons advocate complete abscess evacuation while others advocate repeated aspirations as indicated [29]. In cases with multiple abscesses or in those with abscesses in essential brain areas, repeated aspirations are preferred to complete excision. High-dose antibiotics for an extended period may represent an alternative approach in this group of patients and can replace surgical drainage in many other cases.

A long course of antimicrobial treatment of the brain abscess is required because of the prolonged time needed for brain tissue to repair and close the abscess space

[30]. Because of the difficulty involved in the penetration of various antimicrobial agents through the blood–brain barrier, the choice of antibiotics is limited. The antimicrobials advocated for these infections are metronidazole, penicillins, and chloramphenicol.

6.2 Head and Neck Infections

Anaerobic bacteria can be isolated from a variety of these infections and predominate more in the chronic form of these infections. These include chronic otitis media, sinusitis, and mastoiditis; tonsillar, peritonsillar, and retropharyngeal abscesses; all deep neck space infections, thyroiditis, odontogenic infections, and post-surgical and non-surgical head and neck wounds and abscesses. The organisms that are predominant in these infections, *Prevotella*, *Porphyromonas*, *Bacteroides, Fusobacterium*, and *Peptostreptococcus* spp., are all members of the oropharyngeal flora (Table 6).

Most dental infections involve anaerobes. These include endodontal pulpitis and periodontal (gingivitis and periodontitis) infections, periapical and dental abscesses, and perimandibular space infection [31, 32]. Pulpitis may progress to an abscess and eventually involve the mandible and other neck spaces. In addition to the above-mentioned organisms, microaerophilic streptococci and *Streptococcus salivarius* can also be involved.

Vincent's angina (or trench mouth) is a distinct form of ulcerative gingivitis. The causative organisms include *Fusobacterium* species and anaerobic spirochetes; however, definitive studies using anaerobic microbiologic methods remain to be performed.

Deep neck infections generally follow oral, dental, and pharyngeal infections and are generally polymicrobial, involving the anaerobes that caused the primary infections. Mediastinitis following perforation of the esophagus or extension of retropharyngeal abscess or cellulitis, or abscess of dental origin, is most likely to involve mixed aerobic anaerobic infection [33, 34].

Anaerobes have been isolated in 5–15% of patients with acute otitis [35] and 42% of culture-positive aspirates of patients with serous otitis [36]. The predominant isolates in acute otitis were *Peptostreptococcus* spp. and *P. acnes*, and Gram-negative anaerobic bacilli were found in serous otitis media.

Anaerobes were recovered in about 50% of the patients with chronic suppurative otitis media [4, 6, 37, 38] and those with cholesteatoma [39, 40]. The variability in the rate of isolation of anaerobes in these studies may be attributed to differences in the geographic locations and to laboratory methodologies. The predominant anaerobes recovered were Gram-negative bacilli and *Peptostreptococci*, and the aerobes were *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Many of these organisms can produce beta-lactamase and might have contributed to the high failure rate of beta-lactam antibiotics in the therapy of this infection. Anaerobic bacteria were generally recovered, mixed with aerobic bacteria, and the number of isolates per

Table 6 Aerobic and anaerobic bacteria isolated in upper respiratory tract infections

Type of infection	Aerobic and facultative aerobic organisms	Anaerobic organisms
Otitis media: acute	*S. pneumoniae* *Haemophilus influenzae*[a] *M. catarrhalis*[a]	*Peptostreptococcus* spp.
Otitis media: chronic and mastoiditis	*S. aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.
	E. coli[a]	*Bacteroides* spp.[a]
	Klebsiella pneumoniae[a]	*Fusobacterium* spp.[a]
	Pseudomonas aeruginosa[a]	
	Peptostreptococcus spp.	
Peritonsillar and retropharyngeal abscess	*S. pyogenes*	*Fusobacterium* spp.[a]
	S. aureus[a]	*Pigmented Prevotella* and *Porphyromonas* spp.[a]
	S. pneumoniae	
Recurrent tonsillitis	*S. pyogenes*	*Fusobacterium* spp.[a]
	H. influenzae[a]	
	S. aureus[a]	
Suppurative thyroiditis	*S. pyogenes*	*Pigmented Prevotella* and *Porphyromonas* spp.[a]
	S. aureus[a]	
Sinusitis: acute	*H. influenzae*[a]	*Peptostreptococcus* spp.
	S. pneumoniae	
	M. catarrhalis[a]	
Sinusitis: chronic	*S. aureus*[a]	*B. fragilis* group[a]
	S. pneumoniae	*Pigmented Prevotella* and *Porphyromonas* spp.[a]
	H. influenza[a]	
Cervical lymphadenitis	*S. aureus*[a]	*Pigmeted Prevotella* and *Porphyromonas* spp.[a]
	Mycobacterium spp.	*Peptostreptococcus* spp.
Postoperative infection disrupting oral mucosa	*Staphyloccus* spp.[a]	*Fusobacterium* spp.[a]
	Enterobacteriaceae[a]	*Bacteroides* spp.[a]
	Staphylococcus spp.[a]	*Pigmented Prevotella* and *Porphyromonas* spp.[a]
		Peptostreptococcus spp.
Deep neck species	*Streptococcus* spp.	*Bacteroides* spp.[a]
	Staphylococcus spp.[a]	*Fusobacterium* spp.[a]
		Peptostreptococcus spp.[a]
Odontogenic complications	*Streptococcus* spp.	*Pigmented Prevotella* and *Porphyromonas* spp.[a]
	Staphylococcus spp.[a]	*Peptostreptococcus* spp.
Oropharyngeal: Vincent's angina	*Streptococcus* spp.	*F. necrophorum*[a]
Necrotizing ulcerative gingivitis	*Staphylococcus* spp.[a]	*Spirochetes*

[a]Organisms that have the potential of producing beta-lactamase.

specimen ranged between two and six. Anaerobes were isolated from 23 of 24 (96%) specimens of chronic mastoiditis [41] and from most patients with intracranial abscesses that complicate chronic suppurative otitis media [4, 6].

Anaerobic bacteria are often isolated from infected cholesteatomas [39, 40]. Cholesteatoma that often accompanies chronic suppurative otitis media can enhance the absorption of bone, that is enhanced by organic acids produced by anaerobic bacteria [40]. Since cholesteatoma associated with chronic suppurative otitis media contains bacteria similar to those isolated from chronically infected ears, the cholesteatoma may serve as a nidus of the chronic infection.

6.2.1 Sinusitis

In the acute stage of sinusitis the most common pathogens are similar to those recovered in otitis media: *Streptococcus pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. Anaerobic organisms become involved as the infection turns chronic and the levels of tissue oxygen decline [42]. Although anaerobes are generally isolated from only about 10% of patients with acute sinusitis (generally in maxillary sinusitis secondary to periodontal infection), they can be isolated from up to 67% of patients with chronic infection [4, 6]. An average of three anaerobes per sinus aspirate was recovered in patients with chronic sinusitis [43].

The infection may spread via anastomosing veins or contiguously to the central nervous system. Intracranial complications include orbital cellulitis [44], meningitis, cavernous sinus thrombosis, and epidural, subdural, and brain abscesses [4, 6].

6.2.2 Parotitis

Acute suppurative parotitis is generally caused by *S. aureus, Streptococcus* species, and, rarely, aerobic Gram-negative bacteria. Anaerobes, mostly *Peptostreptococcus*, *Bacteroides*, and pigmented *Prevotella* and *Porphyromonas* species, have also been recognized as an important cause of this infection [45]. Empiric antibiotic therapy should be directed against both aerobic and anaerobic bacteria. Surgical drainage may be indicated when pus has formed.

6.2.3 Cervical Lymphadenitis

The most common causes in children are viruses. The organisms that cause acute unilateral infection associated with facial trauma or impetigo are *S. aureus* and *Streptococcus pyogenes*. Cat scratch and mycobacterial infections are important in chronic infections. Anaerobic bacteria have been isolated in about 25% of the infections, often in pure culture [46]; the predominant anaerobes were *Fusobacterium* and *Peptostreptococcus* species. The recovery of anaerobes was often associated with a primary dental, periodontal, or tonsillar infection.

6.2.4 Thyroiditis

Anaerobic bacteria such as anaerobic Gram-negative bacilli and *Peptostreptococcus* species have been identified as causative agents in thyroiditis [4, 6, 47]. *Eikenella corrodens* and *Actinomyces* species have also been reported.

6.2.5 Infected Cysts

Thyroglossal duct cysts, cystic hygromas, branchial cleft cysts, laryngoceles, and dermoid cysts can become inflamed and cause local infection. The organisms that can cause secondary infection of these cysts can originate from either the skin or the oropharynx [48].

6.2.6 Wound Infection After Head and Neck Surgery

These infections are related to the exposure of the surgical site to the oropharyngeal flora and the degree of compromise of the surgical site. Postsurgical head and neck wounds are generally infected by polymicrobial aerobic and anaerobic flora; the number of isolates varies from one to nine (average six) [49]. The most frequently recovered isolates are *Peptostreptococcus* species, *S. aureus*, anaerobic Gram-negative bacilli (i.e., *Bacteroides* species), *Fusobacterium* species, and enteric Gram-negative rods. The presence of polymicrobial flora in postsurgical wounds warrants the use of antimicrobials effective against these organisms in the prophylaxis and therapy of this infection [50].

6.2.7 Tonsillitis

Indirect evidence supports the involvement of anaerobes in acute and chronic tonsillitis. The evidence is mainly derived from studies that show the major role of anaerobes in complications of tonsillitis. The organisms associated with the infection are *Fusobacterium* spp., Gram-negative anaerobic bacilli, and *Peptostreptococcus* spp. Polymicrobial aerobic flora and anaerobic flora predominate in peritonsillar and retropharyngeal abscesses [4, 6, 51]. These organisms can be isolated from 25% of suppurative cervical lymph nodes and are mostly associated with the presence of dental or tonsillar infections [46]. Anaerobic organisms have been associated with thrombophlebitis of the internal jugular veins, which often causes postanginal sepsis [4, 6].

The pathogenic role of anaerobes in the acute inflammatory process in the tonsils is also supported by several clinical observations: their recovery in tonsillar or retropharyngeal abscesses in many cases without any aerobic bacteria [51], the isolation of anaerobes from tonsils in Vincent's angina [4, 6], the recovery of encapsulated pigmented *Prevotella* and *Porphyromonas* species in acutely inflamed tonsils, the isolation of anaerobes from the core of recurrently inflamed non-group A beta-hemolytic streptococcal (GABHS) (*S. pyogenes*) tonsils [52], and the response to antibiotics in patients with non-GABHS tonsillitis [53, 54]. Furthermore, immune

response against *P. intermedia* can be detected in patients with non-GABHS tonsillitis [55]; an immune response can also be detected against *P. intermedia* and *F. nucleatum* in patients who recovered from peritonsillar cellulitis or abscesses [56] and infectious mononucleosis [57].

Therapy with metronidazole alleviated the symptoms of tonsillar hypertrophy and shortened the duration of fever in patients with infectious mononucleosis [53]. Because metronidazole has no antiviral or aerobic antibacterial efficacy, suppression of the oral anaerobic flora may contribute to diminishing the inflammation induced by the Epstein–Barr virus. This is supported by the increased recovery of *P. intermedia* and *F. nucleatum* during the acute phases of infectious mononucleosis [58].

Anaerobes have been isolated from the cores of tonsils of children with recurrent GABHS [59] and non-GABHS tonsillitis [52] and peritonsillar and retropharyngeal abscesses. Beta-lactamase-producing aerobic and anaerobic bacteria were recovered from 75% of tonsils of children with recurrent GABHS tonsillitis [23, 59, 60] and from 40% of those with non-GABHS tonsillitis [52]. Similar organisms were recovered from patients with adenoiditis and adenoid hypertrophy [61].

Recurrent pharyngotonsillitis and penicillin failure to eradicate the GABHS can be a serious clinical problem. One explanation for penicillin failure is that repeated administrations result in selection of beta-lactamase-producing bacteria [23]. The recovery of these bacteria in more than three-quarters of the patients with recurrent GABHS tonsillitis [23, 59, 60], the ability to measure beta-lactamase activity in the core of these tonsils [62], and the response of patients to antimicrobials effective against beta-lactamase-producing bacteria (i.e., clindamycin or amoxicillin plus clavulanic acid) [23, 63, 64] support the role of these beta-lactamase-producing aerobic and anaerobic organisms in the inability of penicillin to eradicate GABHS tonsillitis.

6.3 Pleuropulmonary Infections

Aspiration of oropharyngeal secretions or gastric contents and severe periodontal or gingival disease are the most prevalent risk factors for developing anaerobic pleuropulmonary infection. The infection can progress from pneumonitis into necrotizing pneumonia and pulmonary abscess, with or without empyema. The lesions tend to form in the dependent pulmonary segments, either the superior segments of the lower lobes or the posterior segments of the upper lobes. The infection is generally polymicrobial where the causative organisms of community-acquired infection in 60–80% of cases are members of oropharyngeal flora (Table 7). The predominant anaerobes are *Prevotella*, *Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus* spp., and the aerobic organisms are alpha hemolytic streptococci and microaerophilic streptococci [65]. Anaerobes can be recovered in about a third of children with nosocomial-acquired aspiration pneumonia and pneumonia associated with tracheostomy with and without mechanical ventilation [66] where

Table 7 Aerobic and anaerobic bacteria isolated in different infections

Type of infection	Aerobic and facultative aerobic organisms	Anaerobic organisms
Pleuropulmonary	*Streptococcus viridans*	Pigmented *Prevotella* (*P. denticola, P. melaninogenica, P. intermedia, P. nigrescens, P. loescheii*)
	S. aureus[a]	Nonpigmented *Prevotella* (*P. oris, P. buccae, P. oralis*)
	Enterobacteriaceae[a]	*F. nucleatum* (subsp. *nucleatum*, *polymorphum*)
	P. aeruginosa	*Peptostreptococcus* (*P. micros, P. anaerobius, P. magnus*)
		B. fragilis group
		Non-spore-forming Gram-positive rods (*Actinomyces, Eubacterium, Lactobacillus*)
Intra-abdominal	Intra-abdominal	*B. fragilis* group
	E. coli	*B. wadsworthia*
	Streptococcus (*viridans* group and group D)	*Peptostreptococcus* (especially *P. micros*)
	P. aeruginosa	*Clostridium* spp.
Female genital tract	*Streptococcus* (groups A, B, and others)	*Peptostreptococcus* spp.
	E. coli	*Prevotella* (especially *P. bivia, P. disiens*)
	K. pneumoniae	*B. fragilis* group
	N. gonorrhoeae (in sexually active patients)	*Clostridium* (especially *C. perfringens*)
	Chlamydia (in sexually active patients)	*Actinomyces, Eubacterium* (in intrauterine contraceptive device-associated infections)
	M. hominis (in postpartum patients)	
Skin and soft tissue	*S. aureus*	*Peptostreptococcus* (*P. magnus, P. micros, P. asaccharolyticus*)
	Streptococcus (*S. milleri* group, groups A, B viridans group)	Pigmented *Prevotella* spp.
	Enterococcus spp.[b]	*Actinomyces* spp.
	Enterobacteriaceae[b]	*F. nucleatum*
	P. aeruginosa[a]	*B. fragilis* group[b]
		Clostridium spp.[b]

[a]Recovered in hospital-acquired infection.
[b]After exposure to colonic flora.

they are generally recovered mixed with Enterobacteriaceae, *Pseudomonas* spp., and *S. aureus*. Specimens for culture should be obtained in a fashion that will avoid their contamination by the oral flora. They can be obtained using bronchoalveolar lavage, bronchoscopy via bronchial brush protected in a double lumen-plugged catheter (using quantitative cultures in the last two methods), percutaneous transtracheal aspiration, lung biopsy, and thoracentesis (of empyema fluid). Treatment of these infections include pleural space drainage (in the presence of empyema), and antimicrobials effective against the anaerobic and aerobic bacteria.

6.4 Intra-Abdominal Infections

Secondary peritonitis and intra-abdominal abscesses usually occur because of the entry of enteric bacteria into the peritoneal cavity through a defect in the wall of the intestine or other viscus as a result of obstruction, infarction, or direct trauma. Perforated appendicitis, inflammatory bowel disease with perforation, and gastrointestinal surgery often are associated with polymicrobial synergistic infections caused by aerobic and anaerobic bacteria, where the number of isolates can average 12 (two-thirds are generally anaerobes) (Table 7). Characteristically, the more types of bacteria that can be isolated, the graver the morbidity. The initial infection that follows perforation is peritonitis. The specific microorganisms involved in peritonitis generally are those of the normal flora of the gastrointestinal tract where anaerobic bacteria outnumber aerobes in the ratio 1:1,000–1:10,000 [2]. Of about 400 bacterial species that make the flora, only the virulent ones survive in the peritoneal cavity to cause the infection. The more distal the perforation is in the gastrointestinal tract, the more numerous are the types and number of organisms that spill into the peritoneal cavity.

The predominant aerobic and facultatives are *Escherichia coli*, *Streptococcus* spp. (including *Enterococcus* spp.), and the most frequently encountered anaerobes are the *B. fragilis* group, *Peptostreptococcus* spp., and *Clostridium* spp. [67].

Intra-abdominal infections are typically biphase, where in the initial stages a generalized peritonitis occurs, which is primarily associated with *E. coli* sepsis, and a later phase, where the infection is contained, and intra-abdominal abscesses emerge where *B. fragilis* can be recovered.

Appropriate management of mixed intra-abdominal infections requires the administration of antimicrobials effective against both aerobic and anaerobic components of the infection [4, 6] as well as surgical correction and drainage of pus [8]. Single and easily accessible abscesses can be drained percutaneously, thus avoiding a surgical procedure. The outcome of the infection depends on a variety of factors that include the patient's general condition, the site of performation, the bacteriology of the infection, and the antimicrobial chosen for therapy. The principle of using antimicrobial coverage effective against both aerobic and anaerobic offenders involved in intra-abdominal infections has become the cornerstone of practice and has been confirmed by numerous studies [68].

Therapy should cover Enterobacteriaceae and anaerobes (mainly *B. fragilis* group) and can be achieved by combination or single-agent therapy. Single-agent therapy provides the advantage of avoiding the ototoxicity and nephrotoxicity of aminoglycosides and is less expensive. However, a single agent may not be effective against hospital-acquired resistant bacteria, and the use of a single agent is devoid of antibacterial synergy, which may be important in an immunocompromised host. Combination of therapy can be made of anti-Enterobacteriaceae agent such as an aminoglycoside, a quinolone (in children older than 16 years) or a third-generation cephalosporin, plus anti-anaerobic agent such as clindamycin, metronidazole, or cefoxitin. Single-agent therapy includes a carbapenem (i.e., imipenem and meropenem) or a penicillin plus a beta-lactamase inhibitor (i.e.,

ticarcillin-clavulanate). The need to direct therapy against *Enterococcus* sp. is controversial and some advocate drugs such as ampicillin or vancomycin.

Antimicrobial prophylaxis prior to colonic surgery can reduce the rate of post-surgical wound infection [69]. Therapy includes either oral preparation such as erythromycin and neomycin or parenteral antimicrobial such as cefoxitin.

6.5 Female Genital Tract Infection

These infections can occur in sexually active adolescent females. Genital tract infection involving anaerobes are polymicrobial and include bacterial vaginosis, soft tissue perineal and vulvar and Bartholin gland abscesses, endometritis, pymetra, salpingitis, tubo-ovarian abscesses, adnexal abscess, pelvic inflammatory disease that may include pelvic cellulitis and abscess, amnionitis, septic pelvic thrombophlebitis, intrauterine device-associated infection, septic abortion, and post-surgical obstetric and gynecologic infections (Table 7) [4, 6]. Obtaining proper cultures can be difficult, and avoiding their contamination by the normal genital flora can be achieved by utilization of culdocentesis, laparoscopy, or quantitative endometrial cultures of transcervical samples using a telescoping catheter.

The predominant anaerobic bacteria include *P. bivia* and *P. disiens*, *Peptostreptococcus* spp., *Porphyromonas* spp., and *Clostridium* spp. *Actinomyces* spp. and *Eubacterium nodature* are commonly isolated in infections associated with intrauterine devices. *Mobiluncus* spp. may be involved with bacterial vaginosis [4, 6, 70]. The aerobic organisms also isolated mixed with these anaerobes include Enterobacteriaceae, *Streptococcus* spp. (including group A and B), *Neisseria gonorhoeae* and Chlamydia (in sexually active females), and *Mycoplasma hominis*.

Management of polymicrobial pelvic infection include the use of antimicrobials effective against all potential aerobic and anaerobic pathogens and coverage against sexually transmissible pathogens. The regimens include doxycycline or a macrolide in combination with cefoxitin, cefotetan, clindamycin, or metronidazole.

6.6 Skin and Soft Tissue Infections

Skin and soft tissue infections that can involve anaerobes include superficial infections such as infected cutaneous ulcers, cellulitis, secondary diaper rash, gastrostomy or tracheostomy site wounds, infected subcutaneous sebaceous or inclusion cysts, eczema, scabies or kerion infections, paronychiae, hidradenitis suppurativa, and pyoderma. Subcutaneous tissue infections and post-surgical wound infection that may also include skin involvement include cutaneous and subcutaneous abscesses, decubitus ulcers, breast abscess, bite wound, anaerobic cellulitis and gas gangrene, bacterial synergistic gangrene, infected pilonidal cyst or sinus, and burn wound infection. Deeper situated anaerobic soft tissue infections are necrotizing fasciitis, necrotizing synergistic cellulitis, gas gangrene, and crepitus cellulitis

[71]. These infections can involve only the fascia and/or the muscle surrounded by the fascia (inducing myositis and myonecrosis).

The organisms recovered from soft tissue infections vary according to the type of infections (Table 7). However, the location and the circumstances leading to the infection influence the organisms involved. Cultures often contain several bacterial species that frequently originate from the "normal flora" of the adjacent region.

Wounds and subcutaneous tissue infections and abscesses of the rectal area (decubitus ulcer, perisacral abscess) originate from the gut flora tend to yield organisms found in the colon [4, 6, 72]. These include *B. fragilis* group, *Clostridium* spp., Enterobacteriaceae, and *Enterococci*. In contrast, specimens obtained from sites in and around the oropharynx, or originating from that site, generally contain members of the oral flora (i.e., paronychia and bites). These include pigmented *Prevotella* and *Porphyromonas* spp., *Fusobacterium* spp., and *Peptostreptococcus*. Skin flora organisms such as *S. aureus* and *Streptococcus* spp. or nosocomially acquired organisms (Gram-negative aerobic bacilli) can be isolated at all body sites. In addition to oral flora, human bite infections often contain *Eikenella* and animal bite harbor *Pasteurella multicida* [73].

Infections involving anaerobes are usually polymicrobial and can be complicated by osteomyelitis or bacteremia [74, 75]. Deep tissue infections such as necrotizing cellulitis, fasciitis, and myositis often involve *Clostridium* spp., *S. pyogenes*, and/or polymicrobic combination of aerobic and anaerobic bacteria. They often contain gas in the tissues and putrid-like pus of gray thin quality and can be associated with high rate of bacteremia and mortality [75].

Management of deep-seated soft tissue infection includes surgical de-bridement, drainage and vigorous surgical management. Improvement of oxygenation of the involved tissues through enhancement of blood supply when indicated and administration of HBO especially in clostridial infection may be helpful.

6.7 Osteomyelitis and Septic Arthritis

Anaerobes are especially notable in oesteomyelitis of the long bones after trauma and fracture, osteomyelitis related to peripheral vascular disease, and decubitus ulcers and osteomyelitis of cranial and facial bones. Most of the infections are polymicrobial [74].

Anaerobic osteomyelitis of cranial and facial bones is often secondary to spread of infection from a contiguous soft-tissue source or from sinus, ear, or dental infection. Pelvic osteomyelitis has been related to spread of anaerobes from decubitus ulcers [6]. Osteomyelitis of long bones is generally due to hematogenic spread, trauma, or the presence of a prosthetic device.

Anaerobic streptococci [15] and *Bacteroides* species are the most common organisms at all sites, including bites and cranial infection [73]. Pigmented *Prevotella* and *Porphyromonas* species are especially prevalent in skull and bite infections [12], whereas members of the *B. fragilis* group were associated with

vascular disease or neuropathy. *Fusobacterium* species, which are members of the oral flora, were most frequently isolated from bites and from cranial and facial infections [13]. *Clostridium* species are often found in long bones, especially in association with wound contamination after trauma. Because clostridial species are inhabitants of the lower gastrointestinal tract, they may contaminate compound fractures of the lower extremities.

Septic arthritis due to anaerobic bacteria is uncommon. The role of anaerobes in joint infection was especially obvious in arthritis following hematogenous and contiguous spread of infection, in trauma, and in arthritis associated with prosthetic joints [76]. Most cases of septic arthritis due to anaerobes are monomicrobial.

6.8 Bacteremia

The incidence of anaerobes in bacteremia is 5–15% [75, 77]. *B. fragilis* group is the most prevalent blood culture isolate accounting for over three-quarters of the anaerobic isolates. Other common isolates include *Clostridium* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., and *P. acnes*.

Specific organisms involved in anaerobic bacteremia largely depend on the portal of entry and underlying disease. The predominance of certain isolates in conjunction with the specific sources is related to the origin of the primary infection and the endogenous flora at the anatomic sites. Recovery of *B. fragilis* group organisms and clostridia was mostly associated with a gastrointestinal source, pigmented *Prevotella* and *Porphyromonas* and *Fusobacterium* with oropharynx and pulmonary sources, fusobacteria with the female genital tract, *P. acnes* with foreign body, and peptostreptococci with all sources but especially with oropharyngeal, pulmonary, and female genital tract sources.

The factors predisposing to bacteremia due to anaerobes include neoplasms, hematologic disorders, organ transplant, recent gastrointestinal, obstetric or gynecologic surgery, intestinal obstruction, decubitus ulcers, dental extraction, the newborn age, sickle cell disease, diabetes mellitus, postsplenectomy, and the use of cytotoxic agents or corticosteroids [4, 6].

The clinical presentation of anaerobic bacteremia is similar to aerobic infection except for the signs of infection observed at the infection's port of entry. It commonly includes fever, chills, hypotension, leukocytosis, shock, disseminated intravascular coagulation, and anemia are less infrequent. Features more typical of anaerobic infection include metastatic lesions, hyperbilirubinemia, and suppurative thrombophlebitis. Mortality rate varies between 5 and 10% and is improved with early and appropriate antimicrobial therapy and resolution, when present, of the primary infection.

6.9 Neonatal Infection

The newborn's exposure to the mother's vaginal flora that contains polymicrobial bacterial flora can be associated with the development of anaerobic infection.

These include cellulitis of the site of fetal monitoring (due to *Bacteroides* spp.) [78], neonatal aspiration pneumonia (due to *Bacterodes* spp.) [79], bacteremia [80], conjunctivitis (due to clostridium) [81], omphalitis (due to mixed flora) [82], and infant botulism [83]. Clostridial species may play a role in necrotizing enterocolitis [84].

Management of these infection requires treating the underlying condition(s) and administration of age-adjusted dosages of proper antimicrobial agents.

7 Management

The recovery from an anaerobic infection depends on prompt and proper management. The principles guiding the management of anaerobic infections include neutralizing the toxins produced by anaerobes, preventing their local proliferation by changing the environment, and hampering their spread into healthy tissues.

Toxin neutralization by specific antitoxins may be employed, especially in infections caused by *Clostridium* sp. (tetanus and botulism). Environmental control is achieved by debriding of necrotic tissue, draining the pus, improving circulation, alleviating obstructions, and increasing the tissue oxygenation. Certain types of adjunct therapy such as hyperbaric oxygen (HBO) may also be useful. Antimicrobials' primary role is in limiting the local and systemic spread of the organism. Antimicrobial therapy is in many patients the only form of therapy required, whereas in others it is an important adjunct to a surgical approach.

7.1 Hyperbaric Oxygen

There is controversy whether HBO should be used in infection of spore-forming Gram-positive anaerobic rods. There are several uncontrolled reports that demonstrated efficacy in individual cases [4, 6], however, because no well-controlled studies are available, the use of HBO is unproven. Using HBO in conjunction with other therapeutic measures is not contraindicated except when it may delay the execution of other essential procedures. Topical application of oxygen-releasing compounds may also be useful as an adjunct to other procedures.

7.2 Surgical Therapy

In many cases, surgical therapy is the most important and sometimes the only form of treatment required, whereas in others, surgical therapy is an important adjunct to a medical approach. Surgery is important in draining abscesses, debriding necrotic tissues, decompressing closed space-infections, relieving obstructions, and correcting underlying pathology. When surgical drainage is not used, the infection may persist and serious complications may develop.

7.3 Antimicrobial Therapy

Appropriate management of mixed aerobic and anaerobic infections requires the administration of agents effective against both types of organisms. A number of factors should be considered when choosing appropriate antimicrobial agents. They should be effective against all target organism(s), induce little or no resistance, achieve sufficient levels in the infected site, have safety record and appropriate dosage schedules for children, and have minimal toxicity and maximum stability.

Antimicrobials often fail to cure the infection. Among the reasons for this are the development of bacterial resistance, achievement of insufficient tissue levels, incompatible drug interaction, and the development of an abscess. The environment of an abscess is detrimental to many antibiotics. The abscess capsule interferes with the penetration of drugs, and the low pH and the presence of binding proteins or inactivating enzymes (i.e., beta-lactamase) may impair their activity. The low pH and the anaerobic environment within the abscess are especially unfavorable for the aminoglycosides and quinolones. An acidic pH, high osmolarity, and an anaerobic environment can also develop in an infection site in the absence of an abscess.

When choosing antimicrobials to treat mixed infections, their aerobic and anaerobic antibacterial spectrum (Table 8) and their availability in oral or parenteral form should be considered (Table 9). Some antimicrobials have a limited range of activity. For example, metronidazole is active only against anaerobes and therefore cannot be administered as a single agent for the therapy of mixed infections. Others (i.e., imipenem) have wide spectra of activity against Enterobacteriaceae and anaerobes.

Antimicrobial selection is simplified when reliable culture results are available. However, this may be difficult to achieve because of the problems in obtaining appropriate specimens in anaerobic infections. For this reason, many patients are treated empirically on the basis of suspected rather than known pathogens. Fortunately, the types of anaerobes involved in many anaerobic infections and their antimicrobial susceptibility patterns tend to be predictable, although they may vary in a particular hospital. Some anaerobic bacteria, however, have become resistant to antimicrobial agents or may become so while a patient is receiving therapy.

The susceptibility of the *B. fragilis* group to the frequently used antimicrobial drugs was studied systemically over the past several years. Surveys showed no to minimal resistance to chloramphenicol, metronidazole, imipenem, and the combinations or a penicillin and beta-lactamase inhibitors. However, resistance to other agents varied and the rate differs among various medical centers and generally increases with extensive use of some antimicrobial agents (penicillins, cephalosporins, and clindamycin).

Factors other than susceptibility patterns also influence the choice of antimicrobial therapy. These include the pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity. Although identification of the infecting organisms and their antimicrobial susceptibility may

Table 8 Susceptibility of anaerobic bacteria to antimicrobial agents

Bacteria	Pencillin	A penicillin and a beta-lactamase inhibitor	Ureido- and carobxy-penicillin	Cefoxitin	Chloramphenicol	Clindamycin	Macrolydes	Metronidazole	Carbapenems
Peptostreptococcus sp.	4	4	3	3	3	3	2–3	2	3
Fusobacterium sp.	3–4	3–4	3	3	3	2–3	1	3	3
B. fragilis group	1	4	2–3	3	3	3–4	1–2	4	4
Prevotella and *Porphyromonas* sp.	1–3	4	2–3	3	3	3–4	2–3	4	4
C. perfringens	4	4	3	3	3	3	3	3	3
Clostridium sp.	3	3	3	2–3	3	2	2	3	3
Actinomyces sp.	4	4	3	3	3	3	3	1	3

Degrees of activity: 1, minimal; 2, moderate; 3, good; 4, excellent.

Table 9 Antimicrobial recommended for the therapy of site-specific anaerobic infections

	Surgical prophylaxis	Parenteral	Oral
Intracranial	(1) Penicillin (2) Vancomycin	(1) Metronidazole (4) (2) Chloramphenicol	(1) Metronidazole (4) (2) Chloramphenicol
Dental	(1) Penicillin (2) Erythromycin	(1) Clindamycin (2) Metronidazole (4), chloramphenicol	(1) Clindamycin, amoxicillin + CA (2) Metronidazole (4), chloramphenicol
Upper respiratory tract	(1) Cefoxitin (2) Clindamycin	(1) Clindamycin (2) Chloramphenicol, metronidazole (4)	(1) Clindamycin, amoxicillin + CA (2) Chloramphenicol, metronidazole (5)
Pulmonary	NA	(1) Clindamycin (5) (2) Chloramphenicol, ticarcillin + CA, ampicillin + SU (6), imipenem	(1) Clindamycin (8) (2) Chloramphenicol, metronidazole (5), amoxicillin + CA
Abdominal	(1) Cefoxitin (2) Clindamycin (3)	(1) Clindamycin (3), cefoxitin (3), metronidazole (3) (2) Imipenem, ticarcillin + CA	(1) Clindamycin (8), metronidazole (8) (2) Chloramphenicol, amoxicillin + CA
Pelvic	(1) Cefoxitin (2) Doxycycline	(1) Cefoxitin (6), clindamycin (3) (2) Ticarcillin + CA (6), ampicillin + SU (6), metronidazole (6)	(1) Clindamycin (6) (2) Amoxicillin + CA (6), metronidazole (6)
Skin	(1) Cefazolin (7) (2) Vancomycin	(1) Clindamycin, cefoxitin (2) Metronidazole (4) + methicillin	(1) Clindamycin, amoxicillin + CA (2) Metronidazole (5)
Bone and joint	(1) Cefazolin (7) (2) Vancomycin	(1) Clindamycin, imipenem (2) Chloramphenicol, metronidazole (4), ticarcillin + CA	(1) Clindamycin (2) Chloramphenicol, metronidazole (4)
Bacteremia with BLPB	NA	(1) Imipenem, metronidazole (2) Cefoxitin, ticarcillin + CA	(1) Clindamycin, metronidazole (2) Chloramphenicol, amoxicillin + CA
Bacteremia with non-BLPB	NA	(1) Penicillin (2) Clindamycin, metronidazole, cefoxitin	(1) Penicillin (2) Metronidazole, chloramphenicol, clindamycin

1, drug(s) of choice; 2, alternative drugs; 3, plus aminoglycoside; 4, plus penicillin; 5, plus a macrolide (i.e., erythromycin); 6, plus doxycycline; 7, in location proximal to the reactal and oral areas use cefoxitin; 8, plus a quinolone (only in adults); NA, not applicable; CA, clavulanic acid; SU, sulbactam; BLPB, beta-lactamase-producing bacteria.

be needed for selection of optimal therapy, the clinical setting and Gram-stain preparation of the specimen may suggest what types of anaerobes are present in the infection as well as the nature of the infectious process.

Because anaerobic bacteria generally are recovered mixed with aerobic organisms, selection of proper therapy becomes more complicated. In the treatment of mixed infection, the choice of the appropriate antimicrobial agents should provide for adequate coverage of most of the pathogens.

7.4 Antimicrobial Agents

Some classes of agents possess poor activity against anaerobes. These include the aminoglycosides, the monobactams, and the older quinolones. Antimicrobials suitable to control anaerobic infections are summarized in Tables 9 and 10 and discussed in more detail below [85, 86].

Table 10 Antimicrobial drugs of choice for anaerobic bacteria

	First	Alternate
Peptostreptococcus sp.	Penicillin	Clindamycin, chloramphenicol, cephalosporins
Clostridium sp.	Penicillin	Metronidazole, chloramphenicol, cefoxitin, clindamycin
C. difficile	Vancomycin	Metronidazole, bacitracin
Gram-negative bacilli[a] (BL–)	Penicillin	Metronidazole, clindamycin, chloramphenicol
Gram-negative bacilli[a] (BL+)	Metronidazole, imipenem, a penicillin and beta-lactamase inhibitor, clindamycin	Cefoxitin, chloramphenicol, piperacillin

BL, beta-lactamase.
[a]*B. fragilis* group; *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp.

7.4.1 Penicillins

Penicillin G is the drug of choice against most non-beta-lactamase-producing organisms. These include anaerobic streptococci, *Clostridium* spp., non-sporulating anaerobic bacilli, and most non-beta-lactamase-producing Gram-negative anaerobic rods (i.e., *Bacteroides, Fusobacterium, Prevotella,* and *Porphyromonas* sp.). However, in addition to the *B. fragilis* group, which is known to be resistant to the drug, many other anaerobic Gram-negative rods are showing increased resistance. These include *Fusobacterium*, pigmented *Prevotella* and *Porphyromonas* (common in orofacial and respiratory infections), *P. bivia* and *P. disiens* (prevalent in female genital infections), *Bilophila wadsworthia*, and *Bacteroides splanchinus*.

Resistance to penicillin of some *Clostridium* spp. (*C. ramosum*, *C. clostridioforme*, and *C. butylicum*) through production of beta-lactamase was also noted.

The presence of penicillin-resistant bacteria in an infectious site has important implications for antimicrobial therapy. Many penicillin-resistant anaerobic bacteria can produce enzymes that degrade penicillins or cephalosporins. When such organisms are present in a localized infection, they can release the enzyme into the environment, thus degrading the beta-lactam antibiotic in the area of the infection. Therefore, these organisms may protect not only themselves but also penicillin-sensitive pathogens. Penicillin therapy directed against a susceptible pathogen might therefore be rendered ineffective by the presence of these bacteria [23].

The combinations of beta-lactamase inhibitors (such as clavulanic acid, sulbactam, or tazobactam) plus a beta-lactam antibiotic (ampicillin, amoxicillin, ticarcillin, or piperacillin) can overcome this phenomenon in organisms that produce a beta-lactamase that can be bound by the inhibitor. However, if resistance is due to other mechanisms, blockage of the enzyme beta-lactamase will not prevent resistance. Other mechanisms of resistance are alteration in the porin canal through which the antimicrobial penetrates into the bacteria and changes in the penicillin-binding protein that inhibits introduction of the drug into the cell.

The semisynthetic penicillins, carbenicillin, ticarcillin, piperacillin, and mezlocillin are generally administered in large quantities to achieve high serum concentrations. These drugs have good activity against Gram-negative enterics and most anaerobes in these concentrations. However, these drugs are not entirely resistant to the beta-lactamase produced by Gram-negative anaerobic bacilli.

7.4.2 Cephalosporins

The activity of cephalosporins varies against *Bacteroides* sp. First-generation cephalosporins activity against anaerobes is similar to that of penicillin G, although on a weight basis they are less active. Most strains of the *B. fragilis* group and many *Prevotella* and *Porphyromonas* are resistant because of cephalosporinase production. Cefoxitin is relatively resistant to this enzyme and is the most effective cephalosporin against the *B. fragilis* group and is often used for the therapy and prophylaxis of mixed infections. However, 5–15% of *B. fragilis* group may be resistant, reflecting hospital use pattern. With the exception of *C. perfringens*, cefoxitin is relatively inactive against most species of *Clostridium* (including *C. difficile*). Cefotetan and cefmetazole (also second-generation cephalosporins), have a longer half-life, are as effective as cefoxitin against *B. fragilis*, but have poor efficacy against other members of the *B. fragilis* group (i.e., *B. thetaiotaomicron*). Third-generation cephalosporins are inferior to cefoxitin against *Bacteroides* sp.

7.4.3 Carbapenem (imipenem, meropenem)

The beta-lactam carbapenem have excellent activity against a broad spectrum of aerobic bacteria and anaerobic bacteria, including beta-lactamase-producing *Bacteroides* sp., Enterobacteriaceae, and *Pseudomonas.*

7.4.4 Chloramphenicol

Chloramphenicol has excellent in vitro activity against most anaerobes, and resistance is rare. The drug also is effective against many Enterobacteriaceae and Gram-positive cocci. However, the experience of using this drug in intra-abdominal sepsis was disappointing. The rare but fatal aplastic anemia, the dose-dependent leukopenia, gray syndrome in newborns, and patients with impaired hepatic glucuronidation limit its use.

7.4.5 Clindamycin and Lincomycin

Clindamycin and lincomycin are effective against anaerobes and have good activity against aerobic Gram-positive cocci. Clindamycin has the broader coverage against anaerobes, including beta-lactamase producing *Bacteroides* sp. Resistance of *B. fragilis* group is 5–10%, and some *Clostridium* sp. other than *C. perfringens* are resistant. Antibiotic-associated colitis due to *C. difficile* was first described following clindamycin therapy. However, colitis has been associated with other antimicrobials, and more cases are reported annually following penicillins and cephalosporin therapy than after clindamycin therapy.

7.4.6 Metronidazole

Metronidazole has excellent activity against anaerobes; however, it is not effective against aerobic bacteria. Microaerophilic streptococci*, P. acnes,* and *Actinomyces* sp. often are also resistant. Concern was raised about the carcinogenic and mutagenic effects of this drug; however, these effects were shown only in one species of mice and were never substantiated in other animals or humans [4, 6].

7.4.7 Macrolids (Erythromycin, Azithromycin, Clarithromycin)

Macrolids have moderate-to-good in vitro activity against anaerobic bacteria other than *B. fragilis* and fusobacteria. They are active against *Prevotella* and *Porphyromonas* sp., microaerophilic and anaerobic streptococci, Gram-positive non-spore-forming anaerobic bacilli, and certain clostridia. They show relatively good activity against *C. perfringens* and are poor or inconsistent against Gram-negative anaerobic bacilli.

7.4.8 Glycopeptides (Vancomycin, Teicoplanin)

Vancomycin is effective against all Gram-positive anaerobes (including *C. difficile*) but is inactive against Gram-negative bacilli.

7.4.9 Tetracyclines

Tetracycline is of limited use because of resistance to it by all types of anaerobes including *B. fragilis* group. The newer tetracycline analogues, doxycycline and minocycline, are more active than the parent compound. The use of tetracyclines is not recommended under 8 years of age because of their adverse effect on teeth and bone.

7.4.10 Quinolones

The older quinolones (ciprofloxacin, ofloxacin) are less active than the newer one (trovafloxacin, clinafloxacin) against the *B. fragilis* group. However, the use of the quinolones is limited in growing children because of their possible adverse effects on the cartilage.

7.5 Choice of Antimicrobial Agents

The parenteral antimicrobials that can be used in most infectious sites are clindamycin, metronidazole, chloramphenicol, cefoxitin, a penicillin (i.e., ticarcillin or ampicillin) combined with a beta-lactamase inhibitor (i.e., clavulanic acid or sulbactam), and a carbapenem (i.e., imipenem). An anti-Gram-negative enteric agent (i.e., aminoglycoside) is generally added to clindamycin, metronidazole, and, occasionally, cefoxitin when treating intra-abdominal infections to provide coverage for enteric bacteria. Failure of therapy in intra-abdominal infections has been noticed more often with chloramphenicol and, therefore, this drug is not recommended. Penicillin is added to metronidazole in the therapy of intracranial, pulmonary, and dental infections to cover for microaerophilic streptococci, *Actinomyces* sp., and *Arachnia* sp. A macrolide (i.e., erythromycin) is added to metronidazole in upper respiratory infections to treat *S. aureus* and aerobic streptococci. Penicillin is added to clindamycin to supplement its coverage against *Peptostreptococcus* sp. and other Gram-positive anaerobic organisms (Table 10). Doxycycline is added to most regimens in the treatment of pelvic infections to provide therapy for chlamydia and mycoplasma.

Penicillin is still the drug of choice for bacteremia caused by non-beta-lactamase-producing bacteria. However, other agents should be used for the therapy of bacteremia caused by beta-lactamase-producing bacteria.

The duration of therapy for strict anaerobic infections, which are often chronic, is generally longer than for infections due to aerobic and facultative anaerobes. Oral therapy is often substituted for parenteral therapy after an initial period. The agents available for oral therapy are limited and include clindamycin, amoxicillin plus clavulanic acid, chloramphenicol, and metronidazole.

Clinical judgment, personal experience, safety, and patient compliance should direct the physician in the choice of the appropriate antimicrobial agents. Duration of treatment also must be individualized, depending on the response. In some cases,

such as lung abscesses, treatment may be required for as long as 6–8 weeks but can often be shortened with proper surgical drainage.

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