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Review article

Spectrum and treatment of anaerobic infections

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ABSTRACT

Anaerobes are the most predominant components of the normal human skin and mucous membranes bacterial flora, and are a frequent cause of endogenous bacterial infections. Anaerobic infections can occur in all body locations: the central nervous system, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft tissues. Treatment of anaerobic infection is complicated by their slow growth in culture, by their polymicrobial nature and by their growing resistance to antimicrobials. Antimicrobial therapy is frequently the only form of therapy needed, whereas in others it is an important adjunct to drainage and surgery. Because anaerobes generally are isolated mixed with aerobes, the antimicrobial chosen should provide for adequate coverage of both. The most effective antimicrobials against anaerobes are: metronidazole, the carbapenems (imipenem, meropenem, doripenem, ertapenem), chloramphenicol, the combinations of a penicillin and a beta-lactamase inhibitors (ampicillin or ticarcillin plus clavulanate, amoxicillin plus sulbactam, piperacillin plus tazobactam), tigecycline, cefoxitin and clindamycin.

Contents

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1. Introduction

Infections caused by anaerobic bacteria occur frequently, and can be serious and life-threatening. Because anaerobes colonize the skin and are the main component of mucous membranes flora [1] they are endogenous in nature. Because of their fastidiousness, anaerobes are difficult to isolate and are often unrecognized. Delay in implementing appropriate therapy may lead to clinical failures. Their isolation requires proper methods of collection, transportation and cultivation of specimens [2–6]. Treatment is complicated by their slow in-vitro growth, the infection's polymicrobial nature and the organisms' mounting antimicrobial resistance.

This review describes the clinical spectrum and treatment of anaerobic infections.

2. Microbiology

The clinically important anaerobes accounting to over 95% of infections are:

- Gram-negative rods (*Bacteroides, Prevotella, Porphyromonas, Fusobacterium, Bilophila* and *Sutterella* spp.);
- Gram-positive cocci (mainly *Peptostreptococcus* spp.);
- Gram-positive spore-forming (*Clostridium* spp.) and no spore-forming bacilli (*Actinomyces, Propionibacterium, Eubacterium, Lactobacillus* and *Bifidobacterium* spp.);
- Gram-negative cocci (mainly *Veillonella* spp.) (Table 1) [4–6].

The recovery of anaerobes differs in various infectious sites (Table 2). Polymicrobial infections caused by aerobic and anaerobic organisms are common [2,3].

Anaerobes taxonomy has changed because of improved characterization methods using genetic studies [4,6]. Recent advances in direct detection of anaerobes from clinical samples include 16rRNA gene based methods, DNA hybridization, Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) Biotyper, multiplex PCR and oligonucleotide array technologies [5]. The ability to differentiate between similar strains enables better characterization of types of infection and anticipate antimicrobial susceptibility [4].

Anaerobic spore-forming bacilli belong to the genus Clostridium. They are highly pleomorphic, ranging from short, thick bacilli to long filamentous forms, and are either ramrod straight or slightly curved. The most frequent Clostridia in clinical infections are *Clostridium perfringens, Clostridium septicum, Clostridium ramosum, Clostridium novyi, Clostridium sordellii, Clostridium histolyticum, Clostridium fallax, Clostridium bifermentans and Clostridium innocuum*[4–6].

C. perfringens is an often encapsulated stout gram-variable rods of varying length, found in soil and humans and animals intestines. It is the most commonly isolated histotoxic clostridia and produces several necrotizing extracellular toxins. It can cause devastating illness with high mortality rate and bacteremia associated with extensive tissue necrosis, hemolytic anemia and renal failure.

C. septicum infection (mostly blood and subcutaneous tissue) is often association with occult colonic malignancy. *C. sordellii*

Table 1
Predominant 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 nonspore-forming bacilli	*Propionibacterium* spp.: *P. acnes, P. propionicum, P. granulosum Eubacterium tentum* *Bifidobacterium* spp.: *B. eriksonii, B. dentium* *Actinomyces* spp.: *A. israelii, A. naestundii, A. viscosus, A. odontolyticus, A. meyerii*
Gram-positive spore-forming bacilli	*Clostridium* spp.: *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* spp.: *B. gracilis, B. ureolyticus, Bilophila wadsworthia, Sutterella* spp., 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* spp.: *F. nucleatum, F. necrophorum, F. gonidiaformans, F. naviforme, F. mortiferum, F. varium*

Table 2
Anaerobic bacteria most frequently encountered in specific infection sites.

Organism		Infection site
Gram-positive cocci	*Peptostreptococcus* spp.Microaerophilic streptococci (not obligate anaerobes)	Respiratory tract, intra-abdominal and soft-tissue infections Sinusitis, brain abscesses
Gram-positive bacilli	Nonspore-forming:	Intracranial abscesses, chronic mastoiditis, aspiration pneumonia, head and neck infections
	Actinomyces spp.	Shunt infections (cardiac, intracranial), infections associated with foreign body
	Propionibacterium	Chronic otitis media, cervical lymphadenitis, abdominal infections
	Bifidobacterium spp.	
	Acnes	
	Spore-forming:	Soft-tissue infection, sepsis, food poisoning
	Clostridium perfringens	
	Clostridium septicum	Sepsis, neutropenic enterocolitis
	Clostridium difficile	Colitis, antibiotic-associated diarrheal disease
	Clostridium botulinum	Botulism
	Clostridium tetani	Tetanus
	Clostridium ramosum	Soft-tissue infections
Gram-negative bacilli	*Bacteroides fragilis* group	Intra-abdominal and female genital tract infections, sepsis, neonatal infections
	Pigmented	Orofacial infections, aspiration pneumonia, periodontitis
	Prevotella and *Porphyromonas* spp.	Orofacial infections
	Prevotella oralis, Prevotella oris-buccae,	Orofacial infections, intra-abdominal infections
	Prevotella bivia, Prevotella disiens,	Female genital tract infections
	Fusobacterium nucleatum,	Orofacial and respiratory tract infections, brain abscesses, bacteremia
	Fusobacterium necrophorum	Aspiration pneumonia, mastoiditis, Lemiere's Syndrome, bacteremia

infections often follows abortion, childbirth, and injection drug use [4-6].

C. botulinum can cause four syndromes: foodborne, wound, infant botulism, and adult intestinal toxemia. All of these produce the same clinical syndrome of symmetrical cranial nerve palsies followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. Proteolytic strains of types A and B have been reported from food poisoning and wound infections. Infant botulism occurs with types A, B and F.7 Disease caused by C. botulinum is usually an intoxication produced by ingestion of contaminated food (uncooked meat, poorly processed fish, improperly canned vegetables) containing a highly potent neurotoxin. *C. difficile* causes antibiotic-associated and spontaneous diarrhea and colitis. *C. tetani* is found in soil and rarely human feces. Infections can result from wound contamination with soil containing *C. tetani* spores that germinate in devitalized tissue and produce a neurotoxin [4-6].

Anaerobic Gram-positive, nonspore-forming rods are part of gingival crevices, gastrointestinal tract, and vaginal and the skin flora. They include Propionibacterium, Eubacterium, Bifidobacterium, Lactobacillus. Actinomyces, Arcanobacterium, Atopobium, Mobiluncus, and Pseudoramibacter.

The *Actinomyces, Arcanobacterium and Bifidobacterium* spp. are Gram-positive, pleomorphic, anaerobic to microaerophilic bacilli. *Actinomyces israelii, Actinomyces naeslundii* and *Propionibacterium propionicum*, members of the oral and throat flora, are the most frequent cause of actinomycosis. They have been isolated from intracranial abscesses, chronic mastoiditis, aspiration pneumonia and peritonitis [4-6]. Actinomycosis usually occur in the face, neck, lungs, pleura and genital and urinary tracts. Bone, pericardial and anorectal lesions and bacteremia are less common, but all tissues may be involved.

Eubacterium and anaerobic lactobacilli are part of the oral, vaginal and gastrointestinal flora. They are common in infections associated with malignancy, surgery, immunodeficiency, diabetes mellitus, foreign body, dental extraction and broad-spectrum antibiotic therapy [4-6].

Propionibacterium spp. ordinarily a non pathogens can cause implanted prostheses or central nervous system (CNS) shunt infection and endocarditis in previously damaged heart valves. They have been recovered from parotid and dental infections, brain abscesses, conjunctivitis associated with contact lens, peritonitis and foreign body and pulmonary infections. *Propionibacterium acnes*, commonest species, can be isolated from blood but is associated only rarely with bacteremia or endocarditis. Because these organisms are part of the normal skin flora, they are often a contaminant. *P. acnes* can cause bacteremia, especially in association with shunt and infections, and plays a role in acne vulgaris.

Among Gram-negative bacilli *Bacteroides fragilis* group are the most recovered Bacteroidaceae in clinical specimens. They resist penicillins, mainly through the production of β-lactamase. They include several members – the most commonly isolated ones are B. fragilis (the most commonly recovered member), *Bacteroides thetaiotaomicron, Bacteroides distasonis, Bacteroides ovatus* and *Bacteroides vulgatus*. They are part of the normal gastrointestinal flora1 and predominate in intra-abdominal infections and other infections that originate from gut flora (i.e. perirectal abscesses, decubitus ulcers) [4-6]The newly defined *Bilophila wadsworthia* and *Centipeda periodontii* are found in abdominal and endodontal infections, respectively.

Pigmented Prevotella (Prevotella melaninogenica, Prevotella intermedia), Porphyromonas (Porphyromonas asaccharolytica) and nonpigmented Prevotella (Prevotella oralis, Prevotella oris) are part of the oral and vaginal flora and are the predominant anaerobic Gram-negative bacilli (AGNB) isolated from respiratory infections and their complications, aspiration pneumonia, lung abscess, chronic otitis media, chronic sinusitis, abscesses around the oral cavity, bite infection, paronychia, brain abscesses and osteomyelitis [4-6]. Prevotella bivia and Prevotella disiens predominate in obstetric and gynecologic infections.

Fusobacterium species are fusiform moderately long and thin organisms with tapered ends. *Fusobacterium nucleatum, Fusobacterium necrophorum, Fusobacterium mortiferum* and *Fusobacterium varium* predominant in oral, pulmonary and intracranial infections. *Fusobacterium* spp. are also isolated from abscesses, obstetric and gynecologic infections, blood and wounds.

A growing resistance of AGNB to penicillins has been noted in recent years.20 Resistance was observed in pigmented Prevotella and Porphyromonas, P. oralis, P. disiens, P. bivia and Fusobacterium spp. The main mechanism of resistance is through β-lactamase production.

The recovery AGNB in infected sites is similar to their distributions in the normal flora [4-6]. *B. fragilis* group were more often found in sites proximal to the gastrointestinal tract, pigmented *Prevotella* spp. were more prevalent in infections proximal to the oral cavity, and *P. bivia* and *P. disiens* were more often isolates in

obstetric and gynecologic ones (Table 2). Familiarity with this mode of distribution enables logical choice of antimicrobials adequate for the treatment of infections in or proximal to these sites.

The predominate Gram-positive cocci are Peptostreptococcus magnus, Peptostreptococcus asaccharolyticus, Peptostreptococcus anaerobius, Peptostreptococcus prevotii and Parvimonas micra (Peptostreptococcus micros). Other anaerobic cocci include Coprococcus, Peptococcus, Ruminococcus sarcina and Staphylococcus saccharolyticus. They are part of the oral, upper respiratory tract, intestinal tract, vagina and skin flora.

These organisms can be isolated in all types of anaerobic infection including respiratory infection (chronic sinusitis, mastoiditis, acute and chronic otitis media, aspiration pneumonia and lung abscess), and necrotizing, subcutaneous and soft-tissue infections [4-6]. They can be isolated alone or mixed with other aerobic or anaerobic organisms. Microaerophilic streptococci are not true anaerobes and can become aerotolerant after subculture. They include Streptococcus anginosus group (previously Streptococcus milleri group, which includes Streptococcus constellatus and Streptococcus intermedius) and Gemella morbillorum (previously Streptococcus morbillorum). Microaerophilic streptococci are common in chronic sinusitis and brain abscesses, obstetric and gynecologic infections and abscesses.

There are three anaerobic **Gram-negative cocci** genera: *Veillonella, Acidaminococcus* and *Megasphaera* spp. *Veillonella* spp., the commonest of the three are members of the oral, vaginal and the small intestinal flora. They are rarely isolated from almost every type of anaerobic infection.

3. Predisposing conditions

These include exposure of a sterile body site to a high inoculum of indigenous mucousal membrane flora, poor blood supply and tissue necrosis favoring the growth of anaerobes. Any condition that lowers the blood supply to an affected area include: trauma, foreign body, malignancy, surgery, edema, shock, colitis and vascular disease. Other conditions include diabetes mellitus, splenectomy, immunosuppression, hypogammaglobinemia, neutropenia, leukemia, collagen vascular disease and cytotoxic drugs. Infection with aerobic or facultative bacteria can favorable for the growth of anaerobes. Anaerobic conditions and anaerobes can impair phagocytosis and intracellular killing [7] and by succinic acid produced inhibition of chemotaxis, degradation of serum proteins by proteases and production of leukotoxins [8].

Suppuration, abscess formation, thrombophlebitis and gangrenous tissue destruction associated with gas formation are the hallmarks of anaerobic infection. Anaerobes are commonly recovered in chronic infections, and after failure of antimicrobial therapy with ineffective agents.

Some infections are likely to include anaerobes. These include brain abscess, oral and dental infections, bites, aspiration pneumonia, lung abscesses, peritonitis after perforation, amnionitis, endometritis, septic abortions, tubo-ovarian abscess, abscesses in and around the oral and rectal areas, pus-forming necrotizing infections of soft tissue or muscle and postsurgical infections [5]. Some solid tumors (i.e., colonic, uterine, bronchial, carcinomas, head and neck) can become infected with anaerobes [9].

4. Prevention

Prevention and early therapy of conditions that can lead to anaerobic infection can reduce their rate. Examples include preventing oral flora aspiration by improving neurologic status, suctioning oral secretions, improving oral hygiene, and maintaining lower stomach pH can reduce the risk of aspiration pneumonia and its complications. Irrigation and debridement of wounds and necrotic tissue, drainage of pus, and improvement of blood supply help prevent skin and soft tissue infections [3,5].

Prophylaxis is recommended before surgery when the operative field is expected to be contaminated by mucousal membrane flora. Cefoxitin or ertapenem are used in procedures that involve the oral, rectal or vulvovaginal. Vaccination with tetanus toxin can prevent *C. tetani* infection.

5. Signs and symptoms associated with anaerobic infections

Suppuration, abscess formation, thrombophlebitis and gangrenous destruction of tissue associated with gas formation are the hallmarks of anaerobic infection. Clinical signs of anaerobic infection include:

- Infection adjacent to a mucosal surface
- Foul-smelling discharge
- Necrotic gangrenous tissue and abscess formation
- Free gas in tissue
- Bacteremia or endocarditis with no growth on aerobic blood cultures
- Infection related to the use of antibiotics effective against aerobes only
- Infection related to tumors or other destructive processes
- Infected thrombophlebitis
- Infection after bites
- Black discoloration of exudates containing *P. melaninogenica*, which may fluoresce under ultraviolet light
- 'Sulfur granules' in discharges caused by actinomycosis
- Clinical presentation of gas gangrene

Clinical condition predisposing to anaerobic infection (after maternal amnionitis, perforation of bowel, etc.) Anaerobes are especially common in chronic infections, and are commonly seen after failure of therapy with antimicrobials that are not effective against them, such as aminoglycosides, trimethoprim–sulfamethoxazole (co-trimoxazole) and 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 and dental infections, human and animal bites, aspiration pneumonia and lung abscesses, peritonitis after perforation of viscus, amnionitis, endometritis, septic abortions, tubo-ovarian abscess, abscesses in and around the oral and rectal areas, pus-forming necrotizing infections of soft tissue or muscle and postsurgical infections following procedures on the oral or gastrointestinal tract or female pelvic area [4-6]. Certain solid malignant tumors, such as colon, uterine and bronchogenic carcinomas, and necrotic tumors of the head and neck, can become infected with anaerobes. The anoxic conditions in the tumor and exposure to the endogenous adjacent mucous flora may predispose to these infections.

6. Clinical infections

Anaerobes have been isolated from infections at all sites. However, the frequency and types of isolates vary and depend on the microbial flora at their source or the adjacent mucocutaneous sites.

6.1. Central nervous system (CNS)

These include brain abscess (BA), subdural empyema, epidural abscess and meningitis. BA often originate from ear, mastoid, sinus, oropharynx, dental or lung infection [10]. Ear or mastoid infection tends to spread to the temporal lobe or cerebellum, whereas facial

Table 3
Aerobic and anaerobic bacteria isolated in head and neck and upper respiratory tract infections.

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Otitis media and mastoiditis: acute	*Streptococcus pneumonia*	*Peptostreptococcus* spp.,
Chronic	*Haemophilus influenzae*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Moraxella catarrhalis[a]	*Bacteroides* spp.[a]
	Staphylococcus aureus[a]	*Fusobacterium* spp.[a]
	Escherichia coli[a]	*Peptostreptococcus* spp.
	Klebsiella pneumoniae[a]	
	Pseudomonas aeruginosa[a]	
Peritonsillar and retropharyngeal abscess	*Streptococcus pyogenes*	*Fusobacterium* spp.[a]
	Staphylococcus aureus[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
Recurrent tonsillitis	*Streptococcus pyogenes*	*Fusobacterium* spp.[a]
	Haemophilus influenzae[a]	
	Staphylococcus aureus[a]	
Suppurative thyroiditis	Streptococcus pyogenes	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Staphylococcus aureus[a]	*Peptostreptococcus* spp.
Sinusitis: acute chronic	*Haemophilus influenzae*[a]	*Peptostreptococcus* spp.
	Streptococcus pneumoniae	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Moraxella catarrhalis[a]	*Fusobacterium* spp.[a]
	Staphylococcus aureus[a]	*Bacteroides fragilis* group[a]
	Streptococcus pneumonia	
	Haemophilus influenzae[a]	
Cervical lymphadenitis	*Staphylococcus aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Mycobacterium spp.	*Peptostreptococcus* spp.
Postoperative infection disrupting oral mucosa	*Staphylococcus* spp.[a]	*Fusobacterium* spp.[a]
	Enterobacteriaceae[a]	*Bacteroides* spp.[a]
	Streptococcus pyogenes	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
		Peptostreptococcus spp.
Deep neck abscesses and parotitis	*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 and necrotizing	*Streptococcus* spp.	*Fusobacterium necrophorum*[a]
	Staphylococcus spp.[a]	

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

sinusitis often causes abscess of the frontal lobe. Hematogenous spread often occurs after dental, oropharyngeal or pulmonary infections, and rarely from endocarditis.

Meningitis can follow respiratory or cerebrospinal fluid shunt infection. Shunt infections are generally caused by skin flora (i.e., *P. acnes*) [11] and in ventriculoperitoneal shunts that perforate the gut by enteric organisms (i.e., *B. fragilis*) [12]. *C. perfringens* can cause BA and meningitis after head injuries or after intracranial surgery [2].

The anaerobes generally recovered from BAs complicating respiratory and dental infections include *Prevotella, Porphyromonas, Bacteroides, Fusobacterium* and *Peptostreptococcus* spp. Microaerophilic and other streptococci are also often isolated.

Early administration of antimicrobials at the stage of encephalitis can prevent 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 recommend evacuation of the abscess, whereas others advocate repeated aspirations [13]. The procedures used are aspiration through a burr hole and complete excision after craniotomy. In multiple abscesses or abscesses in essential brain areas, repeated aspirations are preferred. Open craniotomy with, debridement, intraventricular lavage and intraventricular as well as intravenous antibimicrobial(s) are recommended after intraventricular rupture of the abscess. Prolonged high-dose antibiotics is an alternative approach replacing surgical drainage [13]. Antimicrobials with adequate intracranial penetration are advocated for these infections: metronidazole, penicillins, meropenem and chloramphenicol.

6.2. Head and neck and upper respiratory tract

Anaerobes can be recovered from a variety of head and neck and upper respiratory tract infections especially in their chronic forms (Table 3). These include chronic otitis media, sinusitis and mastoiditis, tonsillar, peritonsillar and retropharyngeal abscesses, deep neck space infections, parotitis, sialadenitis, thyroiditis, odontogenic infections, and postsurgical and nonsurgical head and neck wounds and abscesses. The predominant isolates are *Prevotella, Porphyromonas, Bacteroides, Fusobacterium* and *Peptostreptococcus* spp.

Most dental infections involve anaerobes; endodontal (e.g., pulpitis) and periodontal (gingivitis and periodontitis and periimplantitis) infections, periapical and dental abscesses, perimandibular space infection, and postextraction infection [14,15]. Microaerophilic streptococci and *Streptococcus salivarius* can also be involved in dental infections. Vincent's angina is a distinct form of ulcerative gingivitis; the causative organisms include *Fusobacterium* spp. and anaerobic spirochetes [2].

Ludwig angina is a connective tissue infection, of the floor of the mouth, and Lemierre's syndrome is characterized by thrombosis and suppurative thrombophlebitis of the internal jugular vein that is associated with spread of septic emboli to the lungs and other sites [3,5]; *F. necrophorum* is the prevalent species.

Deep neck infections (e.g., mediastinitis following perforation of the esophagus, extension of retropharyngeal abscess or cellulitis, dental abscess) are usually polymicrobial [16].

6.3. Otitis media

Peptostreptococcus spp. and *P. acnes* were found in 5–15% of acute otitis media [17]. These organism and AGNB were present in 42% of culture-positive aspirates of patients with serous otitis media [18].

Anaerobes were recovered in half of the patients with chronic suppurative otitis media [3,5,19,20]. mastoiditis [21] and infected cholesteatomas [22,23]. The infection is often polymicrobial; the

main isolates were AGNB, peptostreptococci, *Pseudomonas aeruginosa,* and *Staphylococcus aureus*. Anaerobes were isolated from 23 out of 24 (96%) specimens of chronic mastoiditis [21] and from most intracranial abscesses complicating chronic suppurative otitis media [3,5,10]. Fusobacterium spp were also isolated from children with acute and chronic mastoiditis [21]. Many of these organisms can produce β-lactamase that may contribute to the high failure rate of β-lactam antibiotics.

6.4. Rhinosinusitis

Streptococcus pneumoniae, Haemophilus influenzae and *Moraxella catarrhalis predominate in* acute sinusitis [17]. The bacterial sinus flora transitions from aerobic to anaerobic when the infection becomes chronic and oxygen levels decline [24,25]. An elevated serum antibody level to prevotella and fusbacterium was demonstrated in patients with chronic sinusitis [26]. Although anaerobes are generally isolated from only about 7% of acute sinusitis (mostly secondary to dental infection), they can be recovered from up to 67% chronic infection [3,5,27,28].

Sinus infection may spread via anastomosing veins or contiguously to the CNS. Complications include orbital cellulitis [29], meningitis, cavernous sinus thrombosis, and epidural, subdural and brain abscesses [3,5].

6.5. Parotitis

Acute suppurative parotitis is caused by aerobic (*S. aureus*, streptococci, Gram-negative bacteria) and anaerobic (*Peptostreptococcus*, *Bacteroides*, and pigmented *Prevotella* and *Porphyromonas* spp.) bacteria [30]. Empiric therapy should be directed against both. Drainage may be indicated when pus has formed.

6.6. Cervical lymphadenitis

The organisms causing acute unilateral infection associated with facial trauma or impetigo are *S. aureus* and group A β-hemolytic streptococci (GABHS). *Bartonella henselae* and mycobacteria are important in chronic infections. Anaerobes (mostly *Fusobacterium* and *Peptostreptococcus* spp.) were isolated in 25% [31], and were associated with dental, periodontal or tonsillar infection.

6.7. Head and neck infection after surgery

These are caused by the surgical site exposure to the oropharyngeal flora. Surgical wounds are generally infected by polymicrobial aerobic and anaerobic flora; the number of isolates varies from one to nine [32]. The commonest isolates are peptostreptococci, *S. aureus*, AGNB, fusobacteria and Enterobacteriaceae.

6.8. Tonsillitis

Clinical and laboratory data supports the role of anaerobes in acute and chronic tonsillitis. Anaerobes were isolated from 25% of suppurative cervical lymph nodes dental and tonsillar infections [31] and internal jugular veins thrombophlebitis causing postanginal sepsis [3,5]. Fusobacteria, peptostreptococci and AGNB play a major role in complications of tonsillitis (i.e. bacteremia, abscesses). Polymicrobial flora predominate in peritonsillar and retropharyngeal abscesses [3,5,33]. Anaerobes were isolated from the cores of tonsils of children with recurrent GABHS [27,34] and non-GABHS tonsillitis [34].

The pathogenic role of anaerobes in tonsillitis is supported by their recovery in tonsillar or retropharyngeal abscesses, often without any aerobic bacteria [34]; isolation in Vincent's angina [5]; recovery of encapsulated prevotella and porphyromonas in inflamed tonsils [35]; isolation from the core of recurrently inflamed non-GABHS tonsils [34]; and response to antibiotics in non-GABHS tonsillitis [36-38].

Immune response against *P. intermedia* can be detected in non-GABHS tonsillitis patients [39] and against *P. intermedia* and *F. nucleatum* after recovery from peritonsillar cellulitis or abscesses [40], and infectious mononucleosis [41].

Metronidazole alleviated the symptoms of tonsillar hypertrophy and reduced fever in infectious mononucleosis [36]. Since metronidazole has no antiviral or aerobic antibacterial efficacy, its suppression of oral anaerobes may reduce their secondary inflammation. This is supported by the increased recovery of *P. intermedia* and *F. nucleatum* during acute phases of mononucleosis [42].

Table 4
Aerobic and anaerobic bacteria isolated in various types of infection.

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Pleuropulmonary	*Staphylococcus aureus** viridans streptococci	Pigmented *Prevotella* spp. (*P. denticola, P. melaninogenica, P. intermedia, P. nigrescens, P. loescheii*)
	*Pseudomonas aeruginosa**	Nonpigmented *Prevotella* spp. *(P. oris, P. buccae, P. oralis)*
	Enterobacteriaceae*	*Fusobacterium nucleatum*
		Peptostreptococcus spp. *(P. micros, P. anaerobius, P. magnus*
		Bacteroides fragilis group,Nonspore-forming Gram-positive rods (*Actinomyces, Eubacterium, Lactobacillus* spp.)
Intra-abdominal	*Escherichia coli*	*Bacteroides fragilis* group
	Enterococcus spp.	*Bilophila wadsworthia*
	*Pseudomonas aeruginosa**	*Peptostreptococcus* spp. (especially *P. micros*)
		Clostridium spp.
Female genital tract	*Streptococcus* (groups A, B, others)	*Peptostreptococcus* spp.
	Escherichia coli	*Prevotella* spp. (especially *P. bivia, P. disiens*)
	Klebsiella pneumonia, Neisseria gonorrhoeae (in sexually active patients)	*Bacteroides fragilis* group
		Clostridium spp. (especially *C. perfringens*)
	Chlamydia spp. (in sexually active patients)	*Actinomyces*
	Mycoplasma hominis (in postpartum patients)	*Eubacterium* spp. (in intrauterine contraceptive device-associated infections)
Skin and soft tissue	*Staphylococcus aureus*	*Peptostreptococcus* spp. (*P. magnus, P. micros,*
	Streptococcus (*Strep. milleri group*, groups A and B, viridans group)	*P. asaccharolyticus*)
		Pigmented *Prevotella* spp., *Actinomyces* spp.
	Enterococcus spp.	Fusobacterium nucleatum†
	Enterobacteriaceae, *Pseudomonas aeruginosa**	*Bacteroides fragilis* group‡ *Clostridium* spp.‡;

* Recovered in hospital -acquired infection + After exposure to oral flora ++ After exposure to colonic flora.

Recurrent pharyngotonsillitis and failure of penicillin to eradicate GABHS can be a serious clinical problem. Penicillin therapy can select BLPB (e.g., prevotella, porphyromonas, fusobacteria, *H. influenza*, *S. aureus)* found in the tonsils of 3/4 of children with recurrent GABHS tonsillitis [27,32,43-45]. The ability to detect β-lactamase in the tonsillar core [46], and the response to antimicrobials effective against BLPB (i.e. clindamycin or amoxicillin/clavulanate) [32,47], highlights the role of aerobic and anaerobic BLPB in the inability of penicillin to eradicate GABHS tonsillitis.

6.9. Pleuropulmonary

Aspiration of oropharyngeal or gastric content, and severe periodontal or gingival disease predispose for anaerobic pleuropulmonary infection. The infection can progress from pneumonitis to necrotizing pneumonia, pulmonary abscess, and empyema [48]. The infection is usually polymicrobial that include *Prevotella, Porphyromonas, Fusobacterium* and *Peptostreptococcus* spp., GABHS and microaerophilic streptococci (Table 4) [49]. Anaerobes were recovered in most community acquired and 1/3 of nosocomial-acquired aspiration pneumonia and pneumonia associated with tracheostomy with and without mechanical ventilation [50].

Adequate cultures should avoid oral flora contamination by 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, or thoracentesis (of empyema fluid). Management includes drainage of empyema, and antimicrobials effective against anticipated anaerobic and aerobic bacteria.

6.10. Intra-abdominal

Most visceral abscesses (e.g., hepatic, splenic); chronic cholecystitis; perforated and gangrenous appendicitis; and perforations resulting from obstruction, inflammatory bowel disease, trauma, diverticulitis, or infarction; postoperative abdominal surgery wound infections and abscesses; are polymicrobial due to gastrointestinal aerobic and anaerobic bacteria [51].

The initial infection following perforation is peritonitis; a synergistic polymicrobial infection [52]. The predominant aerobic and facultatives are *E. coli* and *Streptococcus* spp. (including *Enterococcus* spp.), and the anaerobes are the *B. fragilis* group, and *Peptostreptococcus, Clostridium, Fusobacterium* and *Eubacterium* spp. (see Table 4) [3,5].

Intra-abdominal infections are biphasic: an initial peritonitis associated with *Escherichia coli* sepsis, followed by abscess formation due to anaerobes (mainly *B. fragilis*) [53]. Biliary tract infection is usually caused by *E. coli, Klebsiella* and *Enterococcus* spp. Anaerobes (mainly *B. fragilis* group and rarely *C. perfringens*) can be isolated in infections associated with carcinoma, recurrence, obstruction, bile tract surgery or manipulation [54,55].

Appropriate management of intra-abdominal infections requires administrating antimicrobial effective against both aerobic and anaerobic bacteria [5,56], as well as surgical correction and drainage of pus [56]. Single and easily accessible abscesses can be drained percutaneously. The outcome of the infection depends on a variety of factors that include the general condition of the patient (as measured by the Apache score [57]), site of perforation, bacteriology, and antimicrobials given.

Antimicrobials should cover Enterobacteriaceae and anaerobes (mainly *B. fragilis* group). For mild-to-moderate community-acquired infections in adults, the agents recommended are: ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin. Agents no longer recommended are: cefotetan and clindamycin (because of *B. fragilis* group resistance), ampicillin-sulbactam (*E. coli* resistance) and aminoglycosides (toxicity) [58]. For high risk community-acquired infections in adults, recommended agents are: meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole. Quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones [59].

6.11. Female genital tract

These include soft-tissue and perineal infections; bacterial vaginosis; vulvar and Bartholin gland abscesses; endometritis; pyometra; salpingitis; tubo-ovarian abscesses; adnexal abscess; pelvic inflammatory disease (including pelvic cellulitis and abscess); amnionitis; septic pelvic thrombophlebitis; intrauterine contraceptive device-associated infection; septic abortion; and postsurgical obstetric and gynecologic infections [3,5,60,61]. Avoiding specimen contamination by normal genital flora can be achieved by use of culdocentesis, laparoscopy or quantitative endometrial cultures of transcervical samples.

The predominant anaerobes in these polymcrobial infections include *P. bivia, P. disiens* and *Peptostreptococcus, Porphyromonas* and *Clostridium* spp. [61]. *Actinomyces* spp. and *Eubacterium nodatum* are isolated in infections associated with intrauterine devices. *Mobiluncus* spp. may be involved with bacterial vaginosis [3,5,60]. The isolated aerobes include Enterobacteriaceae, *Streptococcus* spp., *Neisseria gonnorhoeae* and *Chlamydia* spp. and *Mycoplasma genitalium* (see Table 4).

Gas in the tissues, abscess formation and foul-smelling discharge is often associated with the presence of anaerobes. Management includes administration of antimicrobials effective against potential aerobic, anaerobic and sexually transmissible pathogens. Outpatient regimens include cefoxitin, ceftriaxone, or other parenteral third-generation cephalosporins plus doxycycline, with or without metronidazole. In-patient regimens include: cefoxitin, cefotetan, or ampicillin–sulbactam plus doxycycline; and clindamycin or metronidazole plus doxycycline and gentamicin [62].

6.12. Skin and soft-tissue infections

These include superficial infections, such as infected cutaneous ulcers, cellulitis, pyoderma, paronychia, hidradenitis suppurativa and various secondary infected sites. These include secondary infected diaper rash, gastrostomy or tracheostomy site, subcutaneous sebaceous or inclusion cysts, eczema, psoriasis, poison ivy, atopic dermatitis, eczema herpeticum, scabies, kerion, and post-surgical wound [3,5,63-66].

Subcutaneous tissue infections include cutaneous and subcutaneous abscesses, breast abscess, and decubitus ulcers, diabetic (vascular or trophic) ulcers, bite, anaerobic cellulitis, gas gangrene, bacterial synergistic gangrene, infected pilonidal cyst or sinus, Meleney's ulcer and burn [64,66]. Deeper soft-tissue infections include necrotizing fasciitis, necrotizing synergistic cellulitis, gas gangrene and crepitus cellulitis [67]. These infections can involve the fascia and the muscle, and cause myositis and myonecrosis. The isolated bacteria vary according to the type and circumstances leading to the infection, and usually involve members of the normal flora of the region.

Aspirates from wounds and subcutaneous tissue infections and abscesses of the rectal area (i.e., decubitus ulcer, perirectal abscess) or those that originate from the gut flora (i.e. diabetic foot infection) often yield colonic flora [3,5,64-67]. (i.e., *B. fragilis* group, *Clostridium* spp., Enterobacteriaceae, *Enterococcus* spp.). Infections in

and around the oropharynx, or originate from that site (i.e., paronychia, bites, breast abscess), harbor oral flora. (i.e., *Prevotella*, *Porphyromonas, Fusobacterium* and *Peptostreptococcus* spp.). Skin flora (i.e., *S. aureus*, *Streptococcus* spp.) and nosocomially acquired organisms can be found at all body sites (see Table 4). In addition to oral flora, human bite infections often contain *Eikenella* spp. and animal bites harbor *Pasteurella multocida* [68].

These infections are frequently polymicrobial, and in some (i.e., decubitus ulcers, diabetic foot ulcer) complicated by osteomyelitis or bacteremia [69,70]. Deep tissue infections such as necrotizing cellulitis, fasciitis and myositis often involve *Clostridium* spp., *S. pyogenes* or polymicrobic aerobic and anaerobic bacteria. The often have gas in the tissues, putrid-like pus with a gray thin quality, and are associated with a high rate of bacteremia and mortality [67,70].

Management includes surgical debridement, and drainage; improving tissue oxygenation and administration of hyperbaric oxygen (HBO), especially in clostridial infection, may be helpful.

6.13. Osteomyelitis and septic arthritis

Anaerobes are notable in osteomyelitis of cranial and facial bones, long bones following trauma and fracture; and osteomyelitis related to peripheral vascular disease, and decubitus ulcers [69,71]. Cranial and facial bones osteomyelitis is usually caused by oral flora that spread from a contiguous soft-tissue source or from sinus, ear or dental infection. Intestinal anaerobes predominate in pelvic osteomyelitis that spread from decubitus ulcers [5]. Osteomyelitis of long bones is usually caused by hematogenic spread, trauma or the presence of a prosthetic device.

Peptostreptococcus and *Bacteroides* spp. predominate at all sites; *Prevotella* and *Porphyromonas* spp. are prevalent in skull and bite infections, *B. fragilis* group is associated with vascular disease and neuropathy. Fusobacteria are often isolated from bites and cranial and facial infections. Clostridia are found in long bones, especially in association with wound contamination after trauma or exposure to gut flora.

Septic arthritis is rare, and is frequently associated with hematogenous and contiguous spread, trauma and prosthetic joints [69]. Most infections are monomicrobial and the predominant isolates are peptostreptococci and *P. acnes* (often in prosthetic joint infection), *B. fragilis* and fusobacteria (often following hematogenic origin), and clostridia (associated with trauma).

6.14. Bacteremia

The incidence of anaerobes in bacteremia is 5–15% [70]. Recent resurgence in anaerobic bacteremia [72,73] is due to the greater incidence of anaerobic bacteremia in immunosuppressed and those with complex underlying disease [73]. The common isolates are *B. fragilis* group (>75%), *Clostridium* (10–20%), *Peptostreptococcus* (10–15%), and *Fusobacterium* spp. (10–15%) and *P. acnes* (2–5%).

B. fragilis group and clostridia are mostly associated with a gastrointestinal source, pigmented prevotella, porphyromonas and fusobacteria 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.

Predisposing factors include malignancy; hematologic disorders; organ transplant; recent gastrointestinal, obstetric, or gynecologic surgery; intestinal obstruction; decubitus ulcers; dental extraction; the newborn; sickle cell disease; diabetes mellitus; splenectomy; and the use of cytotoxic agents or corticosteroids [3,5].

Typical features include metastatic lesions, hyperbilirubinemia and suppurative thrombophlebitis. Mortality is 15–30% but improves with early and appropriate antimicrobials and resolution of the primary infection.

7. Management

Recovery depends on prompt and proper management. Treatment include neutralizing bacterial toxins produced, preventing local bacterial proliferation by changing the environment and hampering their spread.

Neutralization toxins by specific antitoxins can be employed in clostridial infections (tetanus and botulism). Environmental control is achieved by debriding necrotic tissue, draining pus, improving circulation, alleviating obstructions and increasing tissue oxygenation sometimes by HBO. The primary role of antimicrobials is to limit local and systemic spread of the infection.

7.1. Hyperbaric oxygen

The use of HBO in Gram-positive spore-forming anaerobic rods infection is controversial. Several uncontrolled reports demonstrated efficacy in individual cases [3,5,74], however, since no controlled studies are available, HBO efficacy is unproved. Using HBO along with other therapeutic modalities is not contraindicated, except when it delays other essential procedures.

7.2. Surgical therapy

Surgical therapy is often the most important and sometimes the only required treatment, whereas in others it is an important adjunct to antimicrobials. It is essential to drain abscesses, debride necrotic tissues, decompress closed space infections and relieve obstructions. Without drainage the infection may persist and serious complications can arise.

7.3. Antimicrobial treatment

Appropriate management of mixed aerobic/anaerobic infection requires the administration of antimicrobials active against both components. A number of factors should be considered when choosing appropriate antimicrobials. They should be effective against all targeted organisms, induce minimal or no resistance, achieve adequate levels in the infected site, and induce minimal toxicity.

Antimicrobials may fail to clear the infection because of development of resistance, not achieving sufficient tissue levels, incompatible drug interaction and development of an abscess. Antimicrobials are ineffective in treating abscesses. The abscess capsule reduce their penetration, and the low pH and the presence of binding proteins or inactivating enzymes (i.e. β-lactamase) can impair their activity. Low pH and the anaerobic conditions are detrimental for aminoglycosides and quinolones.

When choosing antimicrobials (see Table 5) for the therapy of polymicrobial infection, their aerobic and anaerobic spectrum and their availability in oral or parenteral form should be considered (Table 6). Some agents possess limited range of efficacy. Metronidazole is effective only against anaerobes and therefore cannot be administered alone for mixed infections. Others (i.e., carbapenems) have broader spectra of activity.

Antimicrobials selection is easier when reliable culture results are available. However, this may be difficult to achieve and most are treated empirically. Fortunately, the types of organism involved in many infections and their antimicrobial susceptibility patterns is predictable. However, antimicrobial resistance patterns may vary and had increased and may emerge during therapy.

Table 5
Activity of antimicrobial agents against anaerobes.

Agent	Comments
Nearly always active	
Metronidazole	Inactive versus microaerophilic streptococci (e.g. *Streptococcus milleri*), *Propionibacterium* and *Actinomyces* spp.; bactericidal versus most Gram-negative anaerobic strains
Carbapenems	Resistant to most *Bacteroides*β-lactamases, although a novel β-lactamase that cleaves carbapenems was found in rare *B. fragilis* strains[a]
β-Lactam plus β-lactamase inhibitors	The addition of a β-lactamase inhibitor to a β-lactam dramatically increases activity against anaerobes that produce a β-lactamase
Chloramphenicol	Good activity versus virtually all clinically significant anaerobes[b]
Usually active	
Clindamycin	*B. fragilis* group: 15–40% of strains resistant; some clostridia other than *C. perfringens* are resistant
Cefamycins	*B. fragilis group*: 5–15% of strains resistant with considerable institutional variation at least partly reflecting use patterns; poor activity versus clostridia
Antipseudomonal	Relatively resistant to β-lactamases of *Bacteroides* spp; penicillins large doses usually employed
Variable activity	
Penicillin	Inactive versus some or most penicillinase-producing anaerobes, including most of the *B. fragilis* group and many strains of *Prevotella melaninogenica, P. intermedia, P. bivia, P. disiens* and some clostridia
Cephalosporins	Less activity *in vitro* than penicillin G versus most anaerobes and limited other than cefamycins published clinical experience to document efficacy
Tetracycline	Inactive versus many anaerobes and most strains of *B. fragilis*; doxycycline and minocycline are somewhat more active than tetracycline
Vancomycin	Active against Gram-positive anaerobes; inactive versus Gram-negative anaerobes
Macrolides	Inactive versus many *Fusobacterium* spp. and some *B. fragilis* spp.; ketolides also show reduced activity versus fusobacteria
Fluoroquinolones	'Third-generation' (gatifloxacin, moxifloxacin and gemifloxacin) show good *in-vitro* activity; limited published data
Tigecycline	Active against nearly all anaerobes including strains of *B. fragilis* that are resistant to β-lactams, clindamycin and quinolones. Minimum inhibitory concentrations are somewhat higher for clostridia[c]
Poor activity	
Aminoglycosides	
Trimethoprim–sulfamethoxazole	
Monobactams (aztreonam)	

[a] Edwards R et al. J Antimicrob Chemother 1999; 43:273–6.
[b] While *in-vitro* activity is excellent, clinical failures with chloramphenicol have been documented, rendering this drug less preferable than other active agents for the treatment of anaerobic infections.
[c] Snydman DR et al. J Antimicrob Chemother 2005; 55:1024–8.

B. fragilis group's susceptibility varies geographically and between institutions, and some antimicrobials used in the past are no longer adequate for empiric therapy [75]. Many AGNB developed resistance to clindamycin, cefoxitin, and cefotetan, but most are uniformly susceptible to metronidazole, carbapenems, and chloramphenicol and the combinations of a beta lactam/beta-lactamase inhibitors [75]. Beta-lactam–beta-lactamase inhibitor combinations maintained good activity against the vast majority of anaerobes; 89% of B. fragilis strains are susceptible to ampicillin-sulbactam, 98% are susceptible to piperacillin-tazobactam.

Table 6
Antimicrobial drugs recommended for the therapy[a] of site-specific anaerobic infections.

	Parenteral	Oral
Intracranial	1. Metronidazole[c] 2. Chloramphenicol	1. Metronidazole[c] 2. Chloramphenicol
Dental	1. Clindamycin 2. Metronidazole[c], Ticarcillin + CA, Ampicillin + SU[e],	1. Clindamycin, Amoxicillin + CA 2. Metronidazole[c]
Upper respiratory tract	1. Clindamycin 2. Ticarcillin + CA, Ampicillin + SU[e], 3. metronidazole[c]	1. Clindamycin, Amoxicillin + CA 2. Metronidazole[d]
Pulmonary	1. Clindamycin[d] 2. Ticarcillin + CA, Ampicillin + SU[e], imipenem or meropenem	1. Clindamycin[f] 2. Metronidazole[d], Amoxicillin + CA
Abdominal	1. Metronidazole[b] 2. Imipenem or meropenem ertapenem, piperacillin-tazobactam, tigecycline, cefoxitin[b]	1. Metronidazole[f] 2. Amoxicillin + CA
Pelvic	1. Cefoxitin[e], clindamycin[b] 2. Piperacillin–tazobactam[e], ampicillin + SU[e], metronidazole[e]	1. Clindamycin[e] 2. Amoxicillin + CA[e], metronidazole[e]
Skin and soft tissue	1. Clindamycin, cefoxitin 2. Metronidazole + vancomycin 3. Tigecycline	1. Clindamycin, amoxicillin + CA 2. Metronidazole + linezolid
Bone and joint	1. Clindamycin, imipenem or meropenem 2. Metronidazole + vancomycin, piperacillin–tazobactam	1. Clindamycin 2. Metronidazole + linezolid
Bacteremia with BLPB	1. Imipenem or meropenem, metronidazole 2. Cefoxitin, ticarcillin + CA	1. Clindamycin, metronidazole 2. Chloramphenicol, amoxicillin + CA
Bacteremia with non-BLPB	1. Penicillin 2. Clindamycin, metronidazole, cefoxitin	1. Penicillin 2. Metronidazole, chloramphenicol, clindamycin

1, Drug(s) of choice; 2, Alternative drugs; In location proximal to the rectal and oral areas use cefoxitin.
[a] Therapies are given as drug(s) of choice (alternative drugs). BLPB, β-lactamase-producing bacteria; CA, clavulanic acid; NA, not applicable; SU, sulbactam.
[b] Plus aminoglycoside.
[c] Plus a penicillin.
[d] Plus a macrolide (i.e. erythromycin).
[e] Plus doxycycline.
[f] Plus a quinolone (only in adults).

Reports of multiple drug resistant *B. fragilis* group underscores the importance of antibiotic stewardship [76,77]. Clinicians can no longer rely on cumulative susceptibility data alone to select antimicrobials and should consider performing susceptibility testing when treating serious infections.

Additional factors influencing antimicrobials choice include: drugs' pharmacology, toxicity, and effect on the flora. Although identification of the pathogen(s) and antimicrobial susceptibility may be required for selection of optimal therapy, the clinical setting and Gram-stain of the specimen may suggest the types of organisms present.

7.4. Antimicrobials

Aminoglycosides, monobactams and older quinolones, possess poor activity against anaerobes. The Agents adequate for treatment of anaerobic infections are discussed below [78,79].

7.4.1. Penicillins

Penicillin G is effective against *Peptostreptocoocus* spp., most *Clostridium* spp. and nonsporulating anaerobic bacilli, and most non-β-lactamase-producing AGNB (i.e., *Bacteroides, Fusobacterium, Prevotella* and *Porphyromonas* spp.) [78]. AGNB that exhibit increased resistance include: *Fusobacterium*, *Prevotella*, and *Porphyromonas* spp., *P. bivia*, *P. disiens*, *Bilophila wadsworthia* and *Bacteroides splanchinus*. Resistance to penicillin by *C. ramosum, C. clostridioforme* and *C. butyricum* through production of β-lactamase has also been observed.

Ampicillin and amoxicillin are equally to penicilin G, but the semisynthetic penicillins are less effective. Methicillin, nafcillin, and the isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin) possess unpredictable activity and are inferior to penicillin G [78,79].

Penicillin therapy might be rendered ineffective by the presence of BLPB [32]. The combinations of β-lactamase inhibitors (e.g., clavulanic acid, sulbactam, tazobactam) with a β-lactam antibiotic (ampicillin, amoxicillin, ticarcillin or piperacillin) can overcome this phenomenon. Other mechanisms of resistance include alteration in the porin canal, and changes in the penicillin-binding protein.

In high concentrations, ticarcillin, piperacillin, and mezlocillin have good activity against Enterobacteriacae and most anaerobes; however, about a third of *B. fragilis* group are resistant [79].

7.4.2. Cephalosporins

First-generation cephalosporins have similar activity against anaerobes as penicillin G. *B fragilis* group, Prevotella, and Porphyromonas resistant first-generation cephalosporins through cephalosporinase production [80]. Cefoxitin is the most effective cephalosporin against the *B fragilis* group, although 5–15% may be resistant. It is not effective against clostridia, except *C. perfringens*. Cefotetan and cefmetazole, a second generation cephalosporins) possess a longer half-life than cefoxitin. They are as effective against *B. fragilis*, but less efficacious against other members of the *B fragilis* group [78,81]. Consequently cefotetan is no longer recommended for treatment of intra-abdominal infections [82].

7.4.3. Carbapenems (imipenem, meropenem, doripenem, ertapenem)

Carbapenems possess excellent activity against aerobic and anaerobic bacteria and are often administered in serious infections. Resistance of *B. fragilis* group is rare (<1%). Carbapenems resistance among anaerobes (1.1–2.5%) was found in a multicenter U.S. survey [75]. A higher rate (7–12%) was noted in a small number of isolates from Taiwan [83]. Ertapenem has similar efficacy but is not active against *Pseudomonas* spp. and *Acinetobacter* spp. [84].

7.4.4. Chloramphenicol

Chloramphenicol has excellent in-vitro activity against most anaerobes, and resistance is uncommon [79]. It lipid solubility enables its penetration across lipid barriers and gaining high CNS concentrations. Its toxicity, the rare but fatal aplastic anemia and the dose-dependent leukopenia, limit its use.

7.4.5. Clindamycin

B. fragilis resistance to clindamycin is increasing worldwide [85] and reached about 40% in some locations [81,82,85]. It is no longer recommended as empiric therapy for intra-abdominal infections.[102] Up to 10% resistance was noted for *Prevotella*, *Fusobacterium*, *Porphyromonas*, and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (mostly *C. difficile*) [79]. Antibiotic-associated colitis due to *C. difficile,* although associated with most antimicrobials, was first described after clindamycin therapy.

7.4.6. Metronidazole and tinidazole

These nitroimidazoles possess excellent activity against anaerobes; however, they are ineffective against aerobes and facultatives. Microaerophilic streptococci, *P. acnes* and *Actinomyces* spp. are often resistant, and adding antimicrobials effective against these organisms is often needed. Resistance among *B. fragilis* group is rare [79]. Concern was raised about the carcinogenicity and mutagenicity of these drugs; however, these effects were found only in a single mice species and were never substantiated in other mammals or humans [3,5].

7.4.7. Macrolides (erythromycin, azithromycin, clarithromycin)

Macrolides have moderate to good activity against anaerobes other than *B. fragilis* group [79]. They are active against pigmented *Prevotella* and *Porphyromonas* spp. and microaerophilic streptococci, Gram-positive non-sporeforming anaerobic bacilli, and certain clostridia. They are less effective against *Fusobacterium* and *Peptostreptococcus* spp. [86]. They are activity against *C. perfringens* and poor or inconsistent activity against AGNB. Clarithromycin is the most active among macrolides against Gram-positive anaerobes, *including Actinomyces, Propionibacterium,* and *Lactobacillus* spp. and *Bifidobacterium dentium*. Emergence of erythromycin-resistant isolates during therapy has been documented [87,88].

7.4.8. Glycopeptides (vancomycin, teicoplanin)

Glycopeptides are effective against Gram-positive anaerobes (including *C. difficile*), and inactive against AGNB [79].

7.4.9. Tetracyclines

Tetracycline is rarely used because of development of resistance by most anaerobes. Resistance to *P. acnes* has been related to previous use [89]. The newer tetracycline analogues doxycycline and minocycline have better efficacy. Because of significant resistance, they can be used only when the isolates are susceptible or in less severe infections where a therapeutic trial is possible.

7.4.10. Tygecycline

This glycylcycline is active against aerobes and anaerobes and certain drug-resistant pathogens [90,91]. It is active against *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *B. fragilis* group, *C. perfringens, C. difficile, and Parvimonas micra* [90,91] Resistance of members of the *B. fragilis* group is 3.3%–7.2% [75].

7.4.11. Fluoroquinolones

Ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin and lomefloxacin are not very active against anaerobes; Sparfloxacin, grepafloxacin. trovafloxacin, gatifloxacin and

Table 7
Antimicrobial drugs of choice for anaerobic bacteria.

	Drug of choice	Alternative drugs
Peptostreptococcus spp.	Penicillin	Clindamycin, chloramphenicol, cephalosporins
Clostridium spp.	Penicillin	Metronidazole, chloramphenicol, cefoxitin, clindamycin
Clostridium difficile	Vancomycin	Metronidazole, bacitracin
Fusobacterium spp.	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL-)	Penicillin	Metronidazole, clindamycin, chloramphenicol
Bacteroides (BL+)	Metronidazole, a carbapenem, a penicillin and β-lactamase inhibitor, clindamycin	Cefoxitin, chloramphenicol, piperacillin, tigecycline

BL- = β -lactamse non producer; BL+ = β -lactamse producer.

moxifloxacin have considerable anti-anaerobic activity; and clinafloxacin and sitafloxacin have the greatest *in-vitro* activity against anaerobes [92]. Moxifloxacin monotherpay has been used in intra-abdominal infections in adults. However, concern over increasing resistance of *E. coli* and *B. fragilis* group reduced its utilizarion [82,92]. Quinolones use is restricted in growing children and during pregnancy because of their possible adverse effects on cartilage.

7.4.12. Other agents

Bacitracin is active against pigmented *Prevotella* and *Porphyromonas* spp. and is inactive against *B. fragilis* and Fusobacteria [2]. Quinupristin–dalfopristin is active against *C. perfringens, Lactobacillus* and *Peptostreptococcus* spp [93]. Linezolid is active against *Fusobacterium, Porphyromonas, Prevotella* and *Peptostreptococcus* spp. [86].

7.5. Choice of antimicrobial agents

Parenteral antimicrobials (Tables 6 and 7) include metronidazole, a penicillin (i.e., ticarcillin, ampicillin, piperacillin) plus a beta-lactamase inhibitor (i.e., clavulanic acid, sulbactam, tazobactam). Agents effective against Gram-negative enteric bacilli (e.g., aminoglycoside, a fluoroquinolone) or an antipseudomonal cephalosporin (e.g., cefepime) are often added to metronidazole for treatment of intra-abdominal infection. Carbapenems (e.g., imipenem, meropenem, doripenem, ertapenem) are utilized as monotherapy [79].

Penicillin can be added to metronidazole in the therapy of intracranial, pulmonary and dental infections to cover microaerophilic streptococci, *Actinomyces* and *Arachnia* spp; A macrolide can be added to penicillin to treat *S. aureus* and aerobic streptococci. Penicillin is added to clindamycin for supplemental coverage against *Peptostreptococcus* spp. and other Gram-positive anaerobes.

Doxycycline is added to most regimens in pelvic infections to cover *Chlamydia* and *Mycoplasma*. Penicillin is still the drug of choice for bacteremia caused by susceptible non-BLPB. However, other agents should be used for the therapy of bacteremia caused by BLPB [3,5].

Because the duration of therapy is often longer than for infections caused by aerobic and facultative bacteria, oral therapy is often substituted for parenteral therapy. The available antimicrobials for oral therapy include amoxicillin plus clavulanic acid, clindamycin, chloramphenicol and metronidazole. The duration of therapy of uncomplicated infection is generally 2–4 weeks. Some infections (i.e., osteomyelitis) require longer treatment. 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.

Clinical judgment, personal experience, safety and patient compliance should direct the physician in the choice of the appropriate antimicrobial agents.

8. Conclusions

Anaerobes are a frequent cause of endogenous infections in all body locations: the central nervous system, oral cavity, head and neck, chest, abdomen, pelvis, skin, and soft tissues. Management of these infection includes administration of effective antimicrobials, surgical drainage and correction of the underlying pathology. Because these infections are often polymicrobial the antimicrobial chosen should provide coverage of both the aerobic and anaerobic component of the infection. The most effective antimicrobials against anaerobes are: metronidazole, the carbapenems (imipenem, meropenem, doripenem, ertapenem), chloramphenicol, the combinations of a penicillin and a beta-lactamase inhibitors (ampicillin or ticarcillin plus clavulanate, amoxicillin plus sulbactam, and piperacillin plus tazobactam), tigecycline, cefoxitin and clindamycin.

Conflict of interest

The author has no conflicts of interest.

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