Anaerobic Infections – A Clinical Overview

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Infections due to anaerobes are common and associated with considerable morbidity and potential mortality. The anaerobic bacteria responsible for disease in humans are to be found in the normal flora of humans and animals and in the environment. Since, in many cases, they are not immediately clinically distinguishable from many other infections, anaerobic infections may readily be overlooked and their diagnosis depends in the first place on a high level of clinical suspicion. If many or most of the anaerobes present are to be cultivated successfully, special precautions are necessary for specimen collection and transport. Though, in principle, the culture and identification of anaerobes is straightforward, the practice requires great attention to technical detail. Anaerobic infections may also be difficult to treat.

Anaerobic Bacteria in Infection

The most important non-sporing anaerobes from the clinical point of view are six genera of Gram-negative rods. Of these Bacteroides spp. (see Chapter 00[103]) are particularly important, especially the species of the B. fragilis group. The other medically important Gram-negative anaerobic genera are Prevotella, Porphyromonas, Fusobacterium, Bilophila and Sutterella. Among the Gram-positive non-sporing anaerobes, there are cocci, primarily Peptostreptococcus, and bacilli of the genera Actinomyces (see Chapter 00[49]), Eubacterium and Propionibacterium and, finally, the Gram-positive spore-forming anaerobic bacilli of the genus Clostridium (see Chapters 00[62], 00[101] and 00[102]). A wide variety of Gram-negative anaerobes (Table 1) and Gram-positive anaerobes (Table 2) are

<table>
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<th>Anaerobic Bacteria in Infection</th>
<th>1</th>
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<td>References</td>
<td>7</td>
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</tbody>
</table>

Table 1 Major anaerobic Gram-negative bacilli encountered in infections

- B. fragilis group
  - Especially B. fragilis, B. thetaotaomicron, B. distasonis, B. ovatus, B. vulgatus
- Other Bacteroides spp.
  - B. splanchnicus, B. ureolyticus
- Porphyromonas spp.
  - Especially P. asaccharolytica, P. gingivalis, P. endodontalis
- Pigmented Prevotella spp.
  - P. corporis, P. denticola, P. intermedia, P. loescheii, P. melaninogenica, P. nigrescens, P. pallens, P. tannerae
- Other Prevotella spp.
  - P. oris, P. buccae, P. oralis group, P. bivia, P. disiens
- Fusobacterium spp.
  - F. nucleatum, F. necrophorum, F. mortiferum, F. varium
- Bilophila wadsworthia
- Sutterella wadsworthensis
- Campylobacter spp.
  - C. curvus, C. gracilis, C. rectus
encountered in clinical specimens, and those most commonly encountered are listed in Table 3. All these organisms are present in the normal flora of humans and animals, and members of the genus *Clostridium* are also present in soils and dust. The bacteriology of the anaerobic bacteria involved in human diseases is described in the standard texts including the following: Shah *et al.* (1998) for *Bacteroides, Prevotella* and *Porphyromonas*, Hofstad (1998) for *Fusobacterium* and *Leptotrichia*; Murdoch (1998) for the Gram-positive anaerobic cocci; and Hatheway and Johnson (1998) for *Clostridium*.

### Pathogenesis of Anaerobic Infection

#### Infections Caused by Non-Sporing Anaerobes

The sources of non-sporing anaerobes that cause infection are the indigenous flora of mucosal surfaces and, to a much lesser extent, that of the skin. Non-sporing anaerobes outnumber aerobes and facultative anaerobes by a ratio of 10:1 in the oral and vaginal floras and by a factor of 1000:1 in the colon. The factors that pre-dispose to anaerobic infection include disruption of normal mucosal or cutaneous barriers by malignant or other disease, surgery, trauma, obstruction of a hollow viscus and presence of a foreign body.

#### Types of Infection

In terms of overall frequency, the four major sites of anaerobic infection are pleuro-pulmonary, intra-abdominal, female genital tract, and skin and soft tissue infections with or without involvement of underlying bone. Examples of other less common infections that primarily involve anaerobic bacteria are brain abscesses and human or animal bite-wound infections. Virtually all types of infection that occur in humans may involve anaerobic bacteria, and no organ or tissue of the body is immune to infection with these organisms. Some common infections that involve non-sporing anaerobic bacteria and the source of infection are listed in Table 4, and their prevalence in some common infections is shown in Table 5. Common characteristics of anaerobic infection are abscess formation and tissue destruction and a tendency to spread to secondary sites by ‘natural routes’, such as in the bloodstream from pelvic sites of infection to the lung or from the pharynx to the middle ear. Septicaemia is a serious complication and may occur at any stage but particularly the late stages of anaerobic infections.

#### Virulence Factors

The variety of different genera and species of non-sporing anaerobes at sites of colonisation far exceeds those isolated from sites of infection. Thus, *Fusobacterium* spp. and of the *Bacteroides* spp. *B. fragilis* are more frequently isolated than other anaerobes. This suggests that specific virulence factors are involved. Indeed, *Prevotella melaninogenica* possesses an antiphagocytic capsule and *B. fragilis* also has a capsule (Kasper, 1976), which acts as a virulence factor (Onderdonk *et al.*, 1977).

Synergy between various anaerobes or between anaerobes and non-anaerobes is often important in mixed anaerobic infections. An example is
post-operative abdominal wound infection after operations in which the bowel has been opened, such as appendicectomy. The bacterial synergy in these infections appears to be a real phenomenon, rather than merely due to inoculum size. Thus, acute ulcerative gingivitis has long been known to be due to synergy between spirochaetes and *Fusobacterium* spp. When both organisms are inoculated into animals lung abscesses can be produced, but each organism alone does not do so (Smith, 1930). More recently evidence has accumulated to show that non-sporing anaerobes in combination with facultative anaerobes are more effective in producing intra-abdominal abscesses than each organism alone (Onderdonk *et al.*, 1976). This may be due to the inhibition of phagocytosis by *B. fragilis* (Ingham *et al.*, 1977). The subject has been reviewed by MacLaren (1997).

As in the case of many other bacteria, some Gram-negative anaerobes adhere to cells by way of fimbriae (Brook and Myhal, 1991). Some other recognised virulence factors are listed in Table 6.

Acute anaerobic infections may become chronic if they are at sites contiguous with anaerobic bacterial colonisation: for example, chronic sinusitis, otitis media, cholecystitis and peritonitis. Acute osteomyelitis, which is usually due to common pyogenic organisms, particularly *Staphylococcus aureus*, has a tendency to become chronic and if anaerobic bacteria are present, for example because of wound contamination, these become involved in the chronic inflammatory process.

Some anaerobic infections, such as lung abscess and actinomycosis, are unique and are readily suspected clinically. Most anaerobic infections are, however, of mixed aerobic and anaerobic aetiology and are not clinically distinctive. Only the foul or putrid odour to a lesion or its discharge is specific, but the other clues may nevertheless be highly suggestive. A simple Gram stain is useful because many anaerobes are morphologically unique. Information obtained in this way about the relative numbers of various organisms may be very useful in directing empirical antimicrobial therapy.

### Infections Caused by Spore-Forming Anaerobes

All the spore-forming anaerobic pathogens belong to the genus *Clostridium*, which also includes many non-pathogenic species that may on occasion be present at sites of infection. The clostridia are principally found in the soil, but some species are present in the bowel flora of humans and animals. From their main habitat in the soil and from faeces the clostridia may be dispersed to other sites and they are present in house dust.

The pathogenic clostridia are responsible for two types of diseases. First the now uncommon histotoxic infections, such as gas gangrene (clostridial
myonecrosis) (see Chapter 00[101]), which occurs after traumatic implantation of the organisms into ischaemic tissues and, second, toxin-induced disease in various target tissues, including the bowel (see below and Chapter 00[62]) and the nervous system (botulism, tetanus) (see Chapters 00[63] and 00[102]).

Wound Infection
Clostridial wound infections occurred in antiquity (Sussman, 1958). Though they are now rare they deserve attention here as a classical example of how the pathogenesis of an infection became understood. Indeed, the mode of action of the α toxin (lecithinase) of Cl. perfringens, which is important in the pathogenesis of gas gangrene, was the first of any exotoxin to be understood in any detail at the molecular level.

Clostridial wound infections first came into prominence during World War I, when the incidence of gas gangrene was extremely high in battle wounds. Since it had been uncommon in earlier wars and was always uncommon in civilian injuries, it came to be regarded as a disease of modern warfare associated with extensive and heavily contaminated wounds. Major wounds of the kind seen in war are uncommon in civilian practice, but gas gangrene can occur in major neglected injuries of any kind if they become contaminated with soil or dust that contains Clostridium spp. Prevention by appropriate surgical treatment and antibiotic prophylaxis is easily available in the developed world, but this is not so in other parts of the world where gas gangrene after accidental trauma is said still to be common.

Three types of clostridial wound are recognised. In increasing order of severity these are: (1) simple contamination in which the organisms are present in the tissues but there is no evidence of infection, (2) clostridial cellulitis in which the infection is localised to skin and soft tissue, the fascia and muscle are not involved and there is little evidence of toxemia, and (3) clostridial myonecrosis in which muscle is involved and there is severe toxemia. If for any reason the tissue oxygen supply is compromised, simple wound contamination may rapidly progress to cellulitis and then to myonecrosis.

Gas gangrene is characteristically associated with serious injuries, but it may follow clean elective surgery and it may rarely follow the injection of adrenaline, which causes vasoconstriction, or insulin into the lower parts of the body, where the skin may be contaminated with the Cl. perfringens derived from the bowel. Criminal instrument-induced abortion used not uncommonly to lead to clostridial infection of the uterus but it is now rare, because of the widespread availability of the legal pregnancy termination. Accounts of clostridial soft-tissue infections have been provided by Lorber (1995), and gas gangrene and related infections have been reviewed by Finegold and George (1989) and Willis (1991). The pathology of gas gangrene has been described by Aikat and Dible (1956, 1960).

Table 6 Some virulence factors of anaerobic non-sporing Gram-negative bacteria (after Lorber, 1995)

<table>
<thead>
<tr>
<th>Virulence factor</th>
<th>Organism</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsular polysaccharide</td>
<td>Bacteroides fragilis</td>
<td>Cell adherence</td>
</tr>
<tr>
<td></td>
<td>Prevotella melaninogenica</td>
<td>Cell adherence</td>
</tr>
<tr>
<td>Fimbriae</td>
<td>B. fragilis group</td>
<td>Adherence to cells and mucus</td>
</tr>
<tr>
<td></td>
<td>Porphyromonas gingivalis</td>
<td></td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>Bacteroides spp.</td>
<td>Lacks Lipid A – low endotoxicity</td>
</tr>
<tr>
<td></td>
<td>Fusobacterium</td>
<td>Potent endotoxic action</td>
</tr>
<tr>
<td>Succinic acid Enzymes</td>
<td>Many species</td>
<td>Inhibition of phagocytosis and intracellular killing</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Bacteroides spp.</td>
<td>Spread in tissues</td>
</tr>
<tr>
<td>Collagenase</td>
<td>Bacteroides spp.</td>
<td>Tissue damage</td>
</tr>
<tr>
<td>Prevotella melaninogenica</td>
<td></td>
<td>Cell membrane damage</td>
</tr>
<tr>
<td>Phospholipase A</td>
<td>Prevotella melaninogenica</td>
<td></td>
</tr>
</tbody>
</table>

Bacteriology The distinction between pathogenic and non-pathogenic Clostridium spp. is that in experimental animals the former can by themselves give rise to clostridial infection, whereas the latter cannot do so, though they render more severe infections by pathogenic species. The principal pathogenic clostridial species responsible for gas gangrene include Cl. perfringens, Cl. novyi, Cl. septicum and C. histolyticum, but other species may also be involved; Cl. sordelli, Cl. sporogenes, Cl. bifermaments and Cl. tertium may also often be present. Since anaerobic infections are often due to wound contamination, they are almost always polymicrobial. In the course
of injury, soil and clothing contaminated with the patient’s own bacterial flora may enter the wound. The clostridia present on clothing consist mainly of \textit{Cl. perfringens} and \textit{Cl. sporogenes}, derived from bowel flora. Surveys during World War I showed that there was a dense and diverse distribution of clostridia in the soil of the Somme and Ypres battlefields, and this was associated with a high incidence of gas gangrene. Similar observations during World War II showed that numbers of anaerobes in desert sands were negligible and gas gangrene was rare (MacLennan, 1943). The clostridial flora of gas gangrene in battle casualties consists mainly of \textit{C. perfringens} and \textit{C. novyi}, but non-clostridial anaerobes and various facultative anaerobes may also be present and facilitate tissue invasion by synergy with histotoxic clostridia. 

Wounds may become contaminated with \textit{Cl. botulinum} but this rarely gives rise to clinical botulism (wound botulism), which when it occurs is usually due to \textit{Cl. botulinum} types A or B. Wound botulism has recently been observed in injecting drug abusers (Asthwal et al., 2000, 2001; Jensenius et al., 2000).

**Pathogenesis** Clostridia do not multiply and cannot produce disease in normal tissues, because the high oxidation–reduction potential (Eh 126–246 mV) of the circulating blood and of the tissues is higher than that necessary for anaerobic bacterial growth (Oakley, 1954). Broth cultures of \textit{Cl. perfringens}, \textit{Cl. septicum} or \textit{Cl. novyi} injected into guineapigs produce a disease similar to gas gangrene, but washed bacilli free of toxins do so only in large numbers. Mixtures of small doses of toxin-free bacilli and sub-lethal doses of culture filtrate are, however, highly virulent. The filtrate allows the bacilli to proliferate in the tissues, produce fresh toxin, and finally kill the animal. The clostridial toxins and other substances in the filtrate interfere with tissue defences and allow the potentially toxigenic bacilli to multiply. The evidence that biologically active clostridial products participate in the pathogenesis of gas gangrene is that (1) the pathogenicity of clostridia correlates with their ability to produce these substances, (2) their injection into tissues mimics the disease and (3) antibodies to these substances is protective. The pathogenesis of experimental gas gangrene has been reviewed by Sussman et al. (1998).

Since clostridia are ubiquitous, most accidental wounds are exposed to the risk of contamination; but since anaerobic conditions do not usually exist in the lesion organisms cannot multiply and gas gangrene does not occur. Tissue anoxia is the central factor that allows anaerobes to grow in wounds. High-velocity missiles cause destructive ‘cavitation’ that reduces tissue perfusion and the shock waves cause damage to distant blood vessels, and this predisposes to anaerobic infections. Missiles may suck in soil, clothing and skin, which carry potential pathogens and bring about deep contamination. Facultative anaerobes, such as \textit{Escherichia coli} and \textit{Proteus} spp., which may also be present in the wound, contribute to the reduction of the local Eh by utilising any remaining oxygen.

Infections that complicate clean elective surgery, such as mid-thigh amputations, are similar to those after accidental trauma. The infecting \textit{Cl. perfringens} is present on the skin and is implanted during surgery. Damaged and anoxic tissues are subject to a rapidly falling Eh, which creates an ideal environment for clostridial growth (Oakley, 1954; Willis, 1969). Bacterial growth is promoted by the production of toxins and products of bacterial metabolism so that gas gangrene becomes established. Under such conditions neither phagocytes nor antibodies can reach the site and the lack of perfusion may prevent antimicrobial agents from reaching adequate concentrations in the affected tissue.

**Clostridial Bacteraemia** Late in the natural history of gas gangrene clostridia involved may invade the bloodstream, and \textit{C. perfringens} bacteraemia may rarely occur after surgery on the gastrointestinal tract, or after perforations of stomach or bowel. Entry of \textit{Cl. perfringens} or \textit{Cl. septicum} into the circulation through a malignant lesion of the colon, probably through an ulcer, is sometimes associated with spontaneous gas gangrene and \textit{Cl. septicum} bacteraemia may spontaneously complicate malignant disease of the colon. \textit{C. septicum} is relatively sparse in the human intestine, and it is not known why it, more often than \textit{C. perfringens} behaves in this way. Clostridial bacteraemia has also been observed in patients with leukaemia.

**Enteric Infections** Mild diarrhoea associated with the consumption of re-heated foods may be due to \textit{Cl. perfringens} present in the food; this is due to certain strains of \textit{Cl. perfringens} type A. This and other clostridial enteric infections are considered in Chapter 00[62].

The association between \textit{Cl. difficile} and antibiotic-associated diarrhoea and pseudomembranous colitis is discussed in Chapter 00[64].

Necrotising jejunitis (enteritis necroticans; pigbel) is a severe and often fatal disease due to \textit{Cl. perfringens} type C. It was first recorded in 1946 in north-west Germany. Severe lower abdominal pain and diarrhoea developed some hours after the patients had eaten rabbit, tinned meat or fish paste and their deaths were
due to peripheral circulatory collapse or intestinal obstruction due to massive jejunal necrosis and mucosal oedema. The disease is referred to as the ‘pigbel’ syndrome, because of its relationship to the widespread practice of pork feasting in New Guinea. It is predominantly an affliction of children and is due to the toxin of Cl. perfringens type C. The organism proliferates in the intestine and releases its toxin, which normally destroyed by intestinal proteinases. The local staple diet of sweet potato contains heat-stable trypsin inhibitors that prevent the destruction of toxin and allow it to damage the bowel. Active immunisation with C. perfringens type C toxoid confers a high degree of lasting protection.

Prevalence

The prevalence of infections involving anaerobes varies considerably according to the nature of the infection. As many as 5% of bacteraemias may be due to these organisms and more than 80% of cerebral abscesses involve anaerobes. Similarly, anaerobic bacteria are involved in the vast majority of neck space infections and infections after head and neck surgery. The prevalence of anaerobes in some sites of normal carriage are given in Tables 7 and 8.

Table 7 Incidence of various Gram-positive anaerobes of the normal flora in humans

<table>
<thead>
<tr>
<th></th>
<th>Clostridium</th>
<th>Actinomyces</th>
<th>Bifidobacterium</th>
<th>Eubacterium</th>
<th>Lactobacillus</th>
<th>Cocci</th>
<th>Propionibacterium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>±</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>±</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mouth</td>
<td>±</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>±</td>
<td>2</td>
</tr>
<tr>
<td>Bowel</td>
<td>2</td>
<td>±</td>
<td>2</td>
<td>2</td>
<td>1–2</td>
<td>±</td>
<td>2</td>
</tr>
<tr>
<td>External genitalia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>U</td>
<td>0</td>
<td>U</td>
<td>1</td>
</tr>
<tr>
<td>Urethra</td>
<td>±</td>
<td>0</td>
<td>0</td>
<td>U</td>
<td>±</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Vagina</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>2</td>
<td>±</td>
<td>2</td>
</tr>
<tr>
<td>Endocervix</td>
<td>±</td>
<td>0</td>
<td>0</td>
<td>±</td>
<td>1</td>
<td>±</td>
<td>2</td>
</tr>
</tbody>
</table>

* Including nasal passages, nasopharynx, oropharynx and tonsils.
U, unknown; 0, not found or rare; ±, irregular; 1, usually present; 2, usually present in large numbers.

Table 8 Incidence of various Gram-negative anaerobes of the normal flora in humans

<table>
<thead>
<tr>
<th></th>
<th>B. fragilis group</th>
<th>Fusobacterium</th>
<th>Other Gram-negative bacilli</th>
<th>Cocci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mouth</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bowel</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>External genitalia</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>1</td>
</tr>
<tr>
<td>Urethra</td>
<td>±</td>
<td>±</td>
<td>1</td>
<td>U</td>
</tr>
<tr>
<td>Vagina</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>1</td>
</tr>
<tr>
<td>Endocervix</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

U, unknown; 0, not found or rare; ±, irregular; 1, usually present; 2, usually present in large numbers.

Specimen Collection and Transport

The proper collection and transport of specimens is crucial for the recovery of anaerobes in the laboratory. Since anaerobes are part of the normal flora, one must be certain not to contaminate the specimens with such flora. This may at times be difficult. A good example of the problem is the patient with suspected aspiration pneumonia. Expectorated sputum would not be suitable because of the large numbers of anaerobes and other organisms present in saliva as indigenous flora. It is, therefore, necessary to ‘bypass’ the normal flora. When there is a collection of pus in a body cavity, such as the chest (empyema), percutaneous needle
aspiration provides a good specimen. If pleural fluid is absent, a suitable fluid can be introduced into the lower respiratory tract through a special double lumen catheter and then removed (bronchoalveolar lavage) for laboratory examination. Alternatively, fluid can be aspirated through a needle introduced into the trachea (tracheal aspiration).

Since many anaerobic bacteria are extremely sensitive to oxygen, proper transport involves placing the specimen into an oxygen-free glass tube or vial under anaerobic conditions in a non-nutritive holding medium for transport to the laboratory.

**Treatment**

The two key approaches to the treatment of all anaerobic infections are surgery and antimicrobial therapy. Typically it is essential to remove infected material surgically (debridement) and to drainage collections of pus or infected exudate. Failure to do so promptly and thoroughly may lead to failure of response to appropriate antimicrobial agents.

Hyperbaric oxygen therapy has revolutionised the treatment of gas gangrene. It consists of exposing the patient to oxygen at a pressure of 2.5–3 atmospheres (25–30 kPa) in specially designed chambers, which had originally been designed to treat deep-sea divers with ‘bends’ (caisson disease). It does not reverse the myonecrosis but it reduces or even stops its progress, so that surgery can be far less radical than would otherwise be necessary. The therapy may also promote the viability of tissues to which the blood supply is otherwise be necessary. The therapy may also promote the viability of tissues to which the blood supply is impaired, and it is often possible to save limbs that would otherwise have had to be amputated. Hyperbaric oxygen directly inhibits the growth of clostridia. It also prevents production of some *Clostridium* toxins and kills vegetative bacilli (Gottlieb, 1971).

Initial antimicrobial therapy is necessarily empirical, since it takes some time to obtain definitive information about the susceptibility of the infecting flora to antimicrobial agents. Antimicrobial resistance is an increasing problem with anaerobic bacteria, and the mechanisms for this resistance are similar to the mechanisms that are involved with non-anaerobes. One of the most common mechanisms of such resistance is β-lactamase production, but this can to some extent be overcome by the use of combinations of β-lactam drugs with various β-lactamase inhibitors. Hyper-production of beta lactamas and production of metalloenzyme β-lactamas may render some of the otherwise better drugs inactive.

The four groups of drugs active almost all anaerobic bacteria are nitroimidazoles, carbapenems, chloramphenicol or thiamphenicol, and combinations of β-lactam drugs with a β-lactamase inhibitor. Non-sporing anaerobic Gram-positive bacilli are commonly resistant to nitroimidazoles. A small numbers of strains of the *Bacteroides fragilis* group may be resistant to all of the above agents except the chloramphenicols.

**References**


Further Reading


