Chapter 1-1. Anaerobic infections (General): epidemiology of anaerobic infections

Introduction

Some anaerobic infections (e.g., tetanus and gas gangrene) are transmitted via environmental factors (soil, etc.), but common types of anaerobic infections occur in the form of endogenous infections caused by indigenous bacterial flora. Search for anaerobes requires special media and culture environments and takes about 1 week. Although attempts have recently been made to develop more rapid anaerobe testing systems facilitating early treatment of anaerobic infections [1], the delay in obtaining culture test results remains an essentially unresolved problem. Gram staining of specimens from patients can yield rapid results, which can be utilized for the diagnosis and treatment of anaerobic infections. However, culture and drug sensitivity test results are obtained much later (mostly after treatment has been started). Thus, the diagnosis and treatment of anaerobic infections still rely heavily on knowledge and experience. This chapter will first briefly characterize infections likely to involve indigenous bacterial flora and anaerobes, as basic knowledge indispensable for understanding anaerobic infections. Then, accounts will be given as to the frequency of anaerobe isolation and the sensitivities of isolated anaerobes to antimicrobial agents, primarily based on laboratory data. Because collected data can vary depending on the testing methods and manipulations, media used, duration of observation, methods adopted for identification, data processing methods, and so on, subsequent discussions will be based on data collected at a single laboratory (Clinical Laboratory of Juntendo University Hospital) to avoid biases stemming from these factors.

Major anaerobes and their sites of colonization

Although most anaerobic infections are caused by indigenous bacteria of the host, the number of frequently detected species as pathogens in anaerobic infections is relatively small [2–5]. Table 1 shows the major anaerobic indigenous bacteria seen in humans. Anaerobes occurring in the highest numbers are Porphyromonas, Prevotella, Fusobacterium (F. nucleatum, etc.), gram-positive cocci such as Peptostreptococcus, and Actinomyces, in the oral cavity and upper airway. These bacteria are frequently isolated as pathogens infecting organs above the diaphragm (brain, spinal cord, neck and lungs). Bacteroides fragilis (B. fragilis) group and Clostridium species constitute a representative bacteria in the large bowel and are isolated from patients with abdominal, gastrointestinal or genital tract infections. Prevotella bivia is often isolated, together with the B. fragilis group, from patients with gynecological infections. Propionibacterium acnes is a representative indigenous bacterium of the skin and is responsible for acne and endophthalmitis after cataract surgery. Finegoldia magna is likely to be misidentified as Staphylococcus spp. when gram stained; it is often isolated from gynecological materials and specimens from skin and soft tissue infections. Adequate knowledge of the common sites of colonization by anaerobes is useful for determining pathogens and estimating their routes of invasion.

Infections often involving anaerobes and infections unlikely to involve anaerobes

There is a report concerning the attempt to classify infections according to the degree of anaerobe involvement...
rated on a four-category scale: (1) very high (frequency of anaerobe isolation ≥70–100%), (2) high (50–100%), (3) low (9–40%) and (4) very rare (<1%). The information shown below, described in this report, may be useful in the diagnosis and treatment of infections [6].

1. Very high (frequency of anaerobe isolation ≥70–100%): gas gangrene, pilonidal cyst, diabetic gangrene/foot ulcers, post-appendectomy infections, infections after colorectal surgery, perianal abscess, lung abscess, nonclostridial crepitant cellulites
2. High (50–100%): aspiration pneumonia/lung abscess, brain abscess, intraperitoneal/pelvic abscess, soft tissue/subcutaneous abscess, dental/oral infections, chronic sinusitis, mammary abscess
3. Low (9–40%): osteomyelitis, bacteremia
4. Very rare (<1%): urinary tract infections

### Epidemiological information on anaerobes derived from laboratory test data

Annual changes in the frequency of anaerobe isolation (during 1994–2003) from clinical materials are shown in Fig. 1 (anaerobes isolated from outpatients) and Fig. 2 (anaerobes isolated from inpatients). Before 1997, anaerobes accounted for 15% or more of all bacteria isolated from outpatients. After 1997, this percentage tended to decrease, reaching about 13% in 2003. The percentage of anaerobes among the bacteria isolated from inpatients has remained at 7–8%, lower than the percentage for outpatients, and there have been no large annual changes in this percentage. The higher percentage of anaerobes isolated from outpatients than inpatients appears to be attributable to the higher number of specimens collected after chemotherapy in the inpatient group than that in the outpatient group. The percentage of anaerobes among all bacteria isolated from outpatients tended to decrease slightly after 2000. This change may be associated with the diminished scale of anaerobe testing aimed at facilitating rapid reporting of test results and minimizing the labor involved in testing. In view of this possibility, data from blood culture tests, involving no such artificial manipulation, are summarized in Fig. 3 [7]. The bar graph in this figure shows the total number of bacteria isolated by blood culture, and the

---

**Table 1** Major anaerobic indigenous bacteria found in humans

<table>
<thead>
<tr>
<th>Site</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach (during hunger)</td>
<td>Genus <em>Lactobacillus</em></td>
</tr>
<tr>
<td>Small intestine (close to center)</td>
<td>Anaerobic streptococcus, <em>Lactobacillus</em> spp.</td>
</tr>
<tr>
<td>Skin</td>
<td><em>Propionibacterium</em> spp., <em>Peptostreptococcus</em> spp.</td>
</tr>
</tbody>
</table>

---

**Fig. 1** Frequency of isolation of bacteria from clinical materials (outpatients)
culturing of the cultured sample are performed as final checks. With the BACTEC System, on the other hand, culture and observation continue for 5 days, and gram staining and subculture are skipped. This difference between the old and new systems may be responsible for the recent decrease in anaerobe isolation. Assuming that isolation of *Propionibacterium* decreased following introduction of the BACTEC System, the decrease may be attributable to the following factors: (1) difference in medium composition, (2) automated detector features, (3) shortened culture period, and so on. It is not known which of these factors, or combinations of factors, is actually responsible for the decrease. In any event, follow-up data in forthcoming years is essential.

Regarding annual changes in anaerobes, the report by Hiramatsu et al. [8] pointed out a marked tendency for a decrease after 1995, and the report by Adachi et al. [9] also demonstrated a trend toward a decrease. In recent years, the scale of anaerobe testing has tended to diminish. In addition to this factor for laboratory procedure, it is noteworthy that the prevalence of anaerobic infection has been decreasing since the introduction of broad-spectrum antimicrobial agents such as carbapenems.

**Frequency of anaerobe isolation for each category of test specimens**

Figures 4 and 5 show the frequency of anaerobe isolation for each category of specimens when anaerobic cultures were conducted [10]. Many of the respiratory specimens found to be anaerobe positive contained pus from patients with peritonsillar abscesses, sputum from patients with aspiration pneumonia, etc. Many of the anaerobes isolated from urogenital organs were associated with infection of female genital organs and their appendages. The frequency

---

**Fig. 2** Frequency of isolation of bacteria from clinical materials (inpatients)

**Fig. 3** Annual changes in the frequency of anaerobe isolation from blood (Modified from Ref. [7])

**Fig. 4** Frequency of anaerobe isolation from each category of test specimens (1994–2003) (Source: Ref. [10])
of anaerobe isolation from respiratory and urogenital specimens was high for outpatients, suggesting that anaerobes are often involved in the primary infection. Anaerobes are rarely isolated in community-acquired pneumonia [11]. The frequency of anaerobe isolation is very high for patients hospitalized with gastrointestinal disease. This is because these inpatients often receive a very high for patients hospitalized with gastrointestinal anaerobes are often involved in the primary infection. Frequency of anaerobe isolation from each category of test specimens (1994–2003) (Source: Ref. [10])

Anaerobes are known to often be isolated from closed pus. Puncture, fistulae and abscesses [10]. The frequency was details of isolation frequency in pus, secretions and puncture fluids. The frequency of anaerobe isolation was high (over 30%) from ascites, fluids collected by Douglas pouch puncture, fistulae and abscesses [10]. The frequency was also high (over 20%) from fluid collected by maxillary sinus puncture, pleural effusion, other puncture fluid and drain fluid. Meanwhile, the frequency was low from synovial fluids, ocular discharge, otorrhea and catheters. Anaerobes are known to often be isolated from closed pus. This is closely related to the previously described “infection involving anaerobes”. It can reasonably be said that anaerobes are often involved in infections of the intraperitoneal cavity, thoracic cavity, female genital organs, skin/soft tissues, nerve tissues (brain, epidural tissue and subdural tissue), oral cavity and neck.

Frequency of isolation of anaerobes analyzed by clinical materials

Figure 6 shows frequency of anaerobes isolated from clinical materials. Of all those isolated, gram-positive and gram-negative anaerobes each accounted for about half. Gram-positive cocci and Prevotella were isolated most frequently (each 22–23%) [10]. Clostridium accounted for 14.1%, most of which was C. difficile isolated from feces of inpatients. Because Prevotella and Porphyromonas take a long time to grow, these anaerobes are seldom detected if anaerobic culture is not continued for more than 48 h. Prevotella and Porphyromonas resemble each other in terms of colony appearance and other morphological features. Many of the anaerobes of these genera are easily detected on anaerobic blood-agar since they form black to brown colonies. However, 4–6 days of observation are needed for their detection. These anaerobes are also occasionally detected in blood culture. Isolation of Porphyromonas is relatively rare. The frequencies of Prevotella and Porphyromonas isolation sometimes differ considerably among laboratories. This variability is often attributable to differences in laboratory procedures (particularly the medium used and the duration of culture). Prevotella and the B. fragilis group are often isolated from patients with infections of the abdomen and female genital organs.

Frequency of isolation of anaerobes analyzed by clinical materials

Figure 7 shows distribution of anaerobes in the clinical materials tested. Gram-positive rods were often isolated from blood, cerebrospinal fluid (CSF) and vascular catheters, and most of them were belonged to Propionibacterium species. Since these anaerobes are known to be representative bacteria constituting indigenous flora of the skin, their detection appears to reflect contamination at the sampling site. Other than these bacteria, Bacteroides (particularly the B. fragilis group) was often isolated from blood. From respiratory organs, Prevotella was often isolated, the B. fragilis group rarely. C. difficile was an overwhelmingly predominant anaerobe isolated from gastrointestinal materials. From urogenital materials, including gynecologic materials, Prevotella was isolated most frequently, and other gram-positive cocci belonging to Peptostreptococcus, etc. were also frequently isolated. Prevotella bivia was often isolated as the pathogen causing
female genital tract infections. Bacteroides was often isolated from pus, secretions, puncture fluids and dialysis fluids. Many of the anaerobes of this genus belonged to the B. fragilis group. The B. fragilis group is representative of anaerobic gram-negative rods. It is often isolated from patients with infections of the abdomen and soft tissue. Figure 8 shows details of isolation frequency among B. fragilis group. B. fragilis accounted for the largest portion (about 40%), followed by B. thetaiotaomicron, B. vulgatus, B. distasonis, B. ovatus, and so on, were isolated as well. B. fragilis group is known to be β-lactamase-producing organisms. They are resistant to ampicillin (ABPC), cefazolin (CEZ), cefotiam (CTM), ceftazidime (CAZ), cefotaxime (CTX), cefpirome (CPR), etc., and are clinically important bacteria. This group of bacteria is easy to culture and grows rapidly. However, their features are quite similar among these bacteria, and sometimes it makes difficult to distinguish the species. Isolation of metallo-β-lactamase-producing bacteria is rare at present, but the clinically isolated bacteria of this type often belong to the B. fragilis.

Figure 9 summarizes the clinical backgrounds of patients whose blood samples were found to contain anaerobes. Of 101 patients, 77.2% had malignant tumors, and 46.5% had diseases of the hepatobiliary system. These findings indicate special attention to anaerobic infections is required when patients have cancer and/or hepatobiliary system disorders.

Susceptibility of anaerobes to antibacterial agents

Gram-positive cocci

Table 2 shows the drug susceptibility rate of anaerobic gram-positive cocci. Streptococcus milleri is a group of microaerophilic bacteria but is listed in this table because it is frequently isolated from anaerobic cultures. In this table, the susceptibility rate means the percentages of strains with MIC under the category of susceptible (S) according to the MIC breakpoint proposed by NCCLS (currently called the Clinical and Laboratory Standards Institutes; CLSI) [12]. For those antibacterial agents for which CLSI breakpoints are not available, susceptibility was determined by referring to the breakpoints for analogous agents. Resistance to penicillin was noted in some strains of Peptostreptococcus anaerobicus but was not seen in the other gram-positive cocci [13]. No strains showed resistant to cephems, carbapenems or vancomycin (VCM). The percentage of erythromycin (EM)-resistant strains was high among gram-positive cocci. The percentage of clindamycin (CLDM)-resistant strains was 10% or higher, although it was not as high as the percentage of EM-resistant strains. On the whole, it is suggested that drug resistant strains was low among gram-positive cocci, except for strains resistant to macrolides (MLs) or CLDM.
Gram-positive rods

Table 3 shows the susceptibility rate of gram-positive rods. *Gardnerella vaginalis* (a bacterium known to grow when incubated in a CO₂ rich atmosphere) was added to this table since it is known to be responsible, like bacteria of *Mobiluncus* species, for bacterial vaginosis. *Eggerthella lenta*, previously known as *Eubacterium lentum*, is often resistant to penicillins (PCs) and cephems, but it is highly sensitive to MLs and CLDM. *C. difficile* is also resistant to many antimicrobial agents other than VCM. *Propionibacterium*, *Atopobium* and *G. vaginalis* are highly sensitive to many antibacterial agents. The susceptibility pattern of *C. difficile* does not differ markedly among different strains, and no strain of this species showed resistant to VCM [14]. Among anaerobic gram-positive rods, *E. lenta* tends to be resistant to β-lactams (BLs), but this species is not frequently isolated from clinical materials, and no case of intractable infection by this bacterium has been encountered at our facility.

Gram-negative rods

Table 4 shows the susceptibility rate of the *B. fragilis* group and Table 5 shows that of the other gram-negative rods to antimicrobial agents. Susceptibility of the *B. fragilis* group is divided into three subgroups ( *B. fragilis*, *B. thetaiotaomicron* and other bacteria). The *B. fragilis* group was often resistant to penicillins and many other cephems, while it was highly sensitive to sulbactam/cefoperazone (SBT/CPZ) and carbapenems. Although the emergence of imipenem (IPM)-resistant strains of the *B. fragilis* group has been attracting close attention, these strains seem to be rare in Japan at present [2, 15, 16]. An increase in strains of the *B. fragilis* group resistant to cefmetazole (CMZ) and CLDM (drugs which have been used in the treatment of *B. fragilis* group infections for many years) has recently been reported. When using these drugs for the treatment of *B. fragilis* group infections, it is essential to conduct a drug sensitivity test and check that the strains in a given case are not resistant to the drugs [17]. The percentage of resistant strains was lower for *Prevotella*, *Porphyromonas* and *Fusobacterium* than for the *B. fragilis* group. *Prevotella bivia*, a β-lactamase-producing bacterium, was often resistant to penicillins and cephems [18].

Conclusion

Recent trends in the isolation of anaerobes and their susceptibilities to drugs have been described above, primarily based on bacteriological testing data. Isolation of anaerobes from clinical materials is apparently decreasing slightly.
Table 3: Drug susceptibility rate of gram-positive rods

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>No. of strains</th>
<th>Benzylpenicillin (penicillin G)</th>
<th>Ampicillin</th>
<th>Piperacillin</th>
<th>Cefazolin</th>
<th>Cefmetazole</th>
<th>Cefotiam</th>
<th>Flomoxef</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Minocycline</th>
<th>Erythromycin</th>
<th>Clindamycin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤32</td>
<td>≤16</td>
<td>≤16</td>
<td>≤16</td>
<td>≤4</td>
<td>≤4</td>
<td>≤0.5</td>
<td>≤2</td>
<td>≤2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. lenta</td>
<td>8</td>
<td>12.5</td>
<td>37.5</td>
<td>100</td>
<td>12.5</td>
<td>87.5</td>
<td>0</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>87.5</td>
<td>100</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>C. difficile</td>
<td>247</td>
<td>ND</td>
<td>65.6</td>
<td>100</td>
<td>4</td>
<td>67.1</td>
<td>0</td>
<td>92.6</td>
<td>44.9</td>
<td>ND</td>
<td>95.9</td>
<td>6.9</td>
<td>14.6</td>
<td>100</td>
</tr>
<tr>
<td>Propionibacterium</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>ssp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobiluncus ssp.</td>
<td>11</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>G. vaginalis</td>
<td>208</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* The numerals below the drug names indicate the MIC breakpoint (μg/mL). CLSI breakpoints are not available for cefazolin, cefotiam, flomoxef, minocycline, erythromycin and vancomycin. Sensitivities to these five drugs were rated on the basis of breakpoints for analogous drugs, if any, or breakpoints available for aerobes.

Table 4: Drug susceptibility rates of Bacteroides fragilis group bacteria

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>No. of strains</th>
<th>Ampicillin</th>
<th>Sulbactam/ampicillin</th>
<th>Piperacillin</th>
<th>Cefazolin</th>
<th>Cefmetazole</th>
<th>Cefotiam</th>
<th>Flomoxef</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Minocycline</th>
<th>Erythromycin</th>
<th>Clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤0.5</td>
<td>≤8/4</td>
<td>≤32</td>
<td>≤16</td>
<td>≤16</td>
<td>≤16</td>
<td>≤4</td>
<td>≤4</td>
<td>≤4</td>
<td>≤0.5</td>
<td>≤2</td>
<td>≤2</td>
</tr>
<tr>
<td>B. fragilis</td>
<td>167</td>
<td>0</td>
<td>95.2</td>
<td>76.6</td>
<td>0</td>
<td>76.8</td>
<td>0</td>
<td>76</td>
<td>98.8</td>
<td>98.8</td>
<td>88.5</td>
<td>4.8</td>
<td>37.1</td>
</tr>
<tr>
<td>B. thitaiotaomicron</td>
<td>82</td>
<td>0</td>
<td>92.4</td>
<td>43.9</td>
<td>0</td>
<td>11.5</td>
<td>0</td>
<td>43.8</td>
<td>96.4</td>
<td>96.4</td>
<td>100</td>
<td>2.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Other Bacteroides</td>
<td>88</td>
<td>10.2</td>
<td>60.2</td>
<td>10.2</td>
<td>82.4</td>
<td>8</td>
<td>69.3</td>
<td>97.7</td>
<td>100</td>
<td>100</td>
<td>15.6</td>
<td>29.5</td>
<td></td>
</tr>
</tbody>
</table>

* The numerals below the drug names indicate the MIC breakpoint (μg/mL). CLSI breakpoints are not available for cefazolin, cefotiam, flomoxef, minocycline and erythromycin. Sensitivities to these five drugs were rated on the basis of breakpoints for analogous drugs, if any, or breakpoints available for aerobes.
However, anaerobes are often involved in infections such as peritonsillar abscesses and both intraperitoneal and uterine appendage infections, and they still play an important role in these infections. Most anaerobic infections are detected in the form of mixed anaerobe-aerobe infections. It is therefore essential to precisely identify the pathogen(s) among the isolated bacteria in individual cases.

The patterns of susceptibility to antimicrobial agent vary among different genera or types of anaerobes, and different from the patterns known for aerobes. These differences must be taken into account. The $B. fragilis$ group has shown the most marked development of drug resistance. At present, the percentage of anaerobe strains resistant to carbapenems is low but the percentage of strains resistant to CLDM is quite high. It is therefore desirable to perform a drug susceptibility test and check that the strains in a given case are not resistant to the drugs.

### References


10. Oguri T. Ideal way of anaerobe testing under the comprehensive medical care—optimum methods of anaerobe testing with cost and profitability taken into account. Nihon Kenkiseikin

---

### Table 5

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>No. of strains</th>
<th>Ampicillin</th>
<th>Sulbactam/ampicillin</th>
<th>Pipertacillin</th>
<th>Cefazolin</th>
<th>Cefmetazole</th>
<th>Cefotiam</th>
<th>Flomoxef</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Minocycline</th>
<th>Erythromycin</th>
<th>Clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella bivia</td>
<td>197</td>
<td>&lt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Prevotella spp.</td>
<td>72</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Porphyromonas spp.</td>
<td>38</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
<td>36</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

* The numerals below the drug names indicate the MIC breakpoint (lg/mL). CLSI breakpoints are not available for cefazolin, cefotiam, flomoxef, minocycline, tetracycline and erythromycin. Sensitivities to these five drugs were rated on the basis of breakpoints for analogous drugs, if any, or breakpoints available for aerobes.


