ABSTRACT

In many respects, anaerobic microbiology has fallen out of the spotlight of infectious diseases, in part due to the extraordinarily successful effort to recognize and treat these infections. Today, anaerobic cultures of clinical specimens are rarely performed and the treatment is fairly standardized. This article reviews the microbiology and pathogenesis of anaerobes, the concept of synergy in mixed infections, and specific anaerobic infections such as lung infections, intra-abdominal sepsis, and female genital tract infections, and a historical overview of the study of anaerobic infection. The more recent developments include some disturbing trends in in vitro sensitivity test results and a continuing controversy about the role of the microbiology lab in these infections.

sensitive forms (few research laboratories could work with anaerobes before this); and 3) clinical studies were spearheaded by Sid Fiengold who devoted his life's work to anaerobic bacteria and "put them on the map." For this, he is often referred to as the Father of the Renaissance. As a result, clindamycin became the drug of choice for anaerobic infections in the United States and metronidazole was used in the United Kingdom.

Table 1 shows an example of the current nomenclature, which has undergone some major changes. For example, Prevotella sp are now the former B melaninogenicus, which is a group of black pigmented strains.

A now-famous paper from John Washington II showed the results of his experience with culturing gram-negative rods in blood. As shown in Table 2, Escherichia coli was the most common, as it was in most other studies from that period; more than half of the cases were due to E coli. Bacteroides bacteremia was second to E coli. Since 1980, Bacteroides bacteremia is rarely seen, testifying to the success of the campaign in the 1970s to raise awareness about anaerobes. B fragilis is recovered so infrequently in blood cultures in the year 2001 that many laboratories are considering discontinuation of the anaerobic blood culture bottle as a method of cost reduction for the laboratory. In fact, the clinical laboratory at Johns Hopkins has an anaerobic chamber plus all of the appropriate equipment for transporting specimens, but still seem to infrequently detect anaerobes.

With that in mind, James Dick, PhD, Associate Professor in the Department of Pathology who also heads the microbiology lab at Johns Hopkins, was asked to record positive blood cultures for E coli and Bacteroides for a period of 1 year. The results were surprising: 22 positive blood cultures for Bacteroides spp from 13 patients, and 192 positive cultures for E coli from 196 patients.

The period of gross neglect in the 1940s through the early 1960s was followed by a period of great emphasis. Many laboratories were doing extensive studies of anaerobic bacteria and the annual meetings of the Infectious Diseases Society of America and the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) were heavily focused on anaerobes—the bacteria, infections, culturing, clinical features, etc. By contrast, there was not a single session at the 40th or 41st ICAAC on anaerobic bacteria or anaerobic infection.

One of the main reasons behind the current shift in emphasis is the existing awareness of anaerobes and...
our success in identifying and treating them. Most infectious disease specialists know that clindamycin should be used to treat a lung abscess, because it is most commonly an anaerobic lung infection and that is the standard treatment. Culturing is not necessary. Because anaerobic bacteriology is not cost effective, there is a movement to eliminate anaerobic culturing in laboratories.

Table 3 outlines how much it costs to identify an anaerobe and conduct sensitivity tests, based on data gathered at Johns Hopkins' laboratories. Included are the labor, reagents, and overhead. Clearly the costs are not enormous, but this is to be part of an overall diminishing emphasis on microbiology, which had, until very recently, become an epidemic in American medicine.

### Anaerobic Microbiology

Anaerobic infections are endogenous; there is only one anaerobic infection that can be transmitted from patient to patient—Clostridium difficile. Most anaerobic infections are polymicrobial, and they often produce gas in the soft tissue and a putrid discharge, at least in the late stages.

Mucosal surfaces such as saliva, teeth, the stomach, ileum, and vagina usually share a 1:1 ratio of anaerobic to aerobic bacteria, although the vagina may have as high as 5 times more anaerobes than aerobes. The gingival crevice and colon have a 1000:1 ratio of anaerobic to aerobic bacteria. So, dental infections and colonic perforation are associated with very high rates of anaerobic infection. Table 4 distinguishes the frequent and rare anaerobic infections. Most anaerobic infections are endogenous, meaning they originate from the host's flora. An exception is urinary tract infections (UTIs). UTIs are endogenous but rarely involve anaerobes. UTIs originate from the urethral flora, which is teeming with anaerobes, but these organisms cannot replicate in the pO₂ of urine. The same applies to spontaneous bacterial peritonitis.

### Pathogenesis

Anaerobes are the primary cause of abscess formation at most anatomic sites (Table 5). The presumed biologic explanation is the capsular polysaccharide which has been studied with B fragilis and appears to be abscessogenic in animals. That is, intraperitoneal abscesses can be produced in ani-

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>Brain abscess</td>
</tr>
<tr>
<td></td>
<td>Dental infections</td>
</tr>
<tr>
<td></td>
<td>Space infections (Chronic sinusitis)</td>
</tr>
<tr>
<td></td>
<td>Chronic otitis</td>
</tr>
<tr>
<td>Chest</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td></td>
<td>Lung abscess</td>
</tr>
<tr>
<td></td>
<td>Empyema</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Peritonitis</td>
</tr>
<tr>
<td></td>
<td>Phlegmon/abscess</td>
</tr>
<tr>
<td>GU tract</td>
<td>Female genital tract</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GU = genitourinary; UTIs = urinary tract infections; STDs = sexually transmitted diseases; SBP = spontaneous bacterial peritonitis.
mals with the injection of capsular material from the B fragilis. Further, Tzianobos et al showed in 1993 that the charge of the B fragilis polysaccharide capsule (i.e., the positively charged amino groups and negatively charged carboxyl or phosphate groups) is critical for this biological result; chemical modification has shown that the oppositely charged groups are an important motif for abscess formation. In their 1994 study, the Salmonella capsule, which normally contains only one carboxyl group, was chemically modified to possess charges which then gave this organism the property of producing abscesses.\textsuperscript{13,14}

Most anaerobic bacteria do not have biologically active endotoxin; the most notable exception is Fusobacterium necrophorum, which is associated with Lemierre's disease and septic shock. B fragilis does not cause septic shock. One common pathogenic mechanism of anaerobes focuses on synergy, because they are usually polymicrobial infections. Synergy is the correlated action of 2 or more organisms—something that cannot be achieved by a single organism. Meleney conducted the sentinel study of anaerobic synergy. He demonstrated that when a mouse is coinfected with S aureus and an anaerobic streptococcus, the characteristic lesion forms. But inoculating with only one or the other organism alone does not produce Meleney's gangrene.\textsuperscript{15}

Does synergy have anything to do with this? A study was conducted in the late 1970s using a Wistar rat model of intra-abdominal sepsis that, following intraperitoneal challenge with the mixed flora of stool, showed that there is an early active peritonitis stage and a late abscess stage (Figure 1). For peritonitis and bacteremia, E coli was critical and for abscess formation B fragilis was critical. There was no synergy. E coli seemed to be totally responsible for the early stage associated with bacteremia and B fragilis was responsible for the late stage with abscess formation.\textsuperscript{16} This was supported by studies of antibiotic probes using gentamicin, showing that gentamicin was active against E coli and clindamycin was active against anaerobes but not active against E coli. Gentamicin reduced mortality but had no effect on abscesses. Clindamycin had no effect on mortality but prevented abscesses (Figure 2).\textsuperscript{17}

**Anaerobic Infections**

**Lung Infections**

The bacteriology of anaerobic pulmonary infections has been studied in more than 300 cases pub-

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequent</th>
<th>Source (Ref. No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>16/18 (89%)</td>
<td>Heineman and Braude 1963\textsuperscript{a}</td>
</tr>
<tr>
<td>Dental</td>
<td>29/31 (94%)</td>
<td>Roser et al 1977\textsuperscript{c}</td>
</tr>
<tr>
<td>Lung</td>
<td>53/39 (93%)</td>
<td>Bartlett et al 1974\textsuperscript{a}</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>67/72 (94%)</td>
<td>Onderdonk et al 1974\textsuperscript{i}</td>
</tr>
<tr>
<td>Tubo-ovarian</td>
<td>32/37 (86%)</td>
<td>Golde et al 1977\textsuperscript{c}</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>81/135 (60%)</td>
<td>Meislin et al 1977\textsuperscript{h}</td>
</tr>
<tr>
<td>Prostatic</td>
<td>16/18 (94%)</td>
<td>Bartlett et al 1981\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Data from references 5-11.

![Figure 1. Stages of Peritoneal Infection](chart)

Data from reference 16.
lished in 2 studies. Of the 865 total anaerobes, the 3 major isolates were pigmented Prevotella (n = 139), Bacteroides spp (n = 117), and peptostreptococci (n = 165). Others included other spp of Prevotella (n = 40), Fusobacteria (n = 90), and Clostridia (n = 30).

**Intra-abdominal Sepsis**

The major anaerobic pathogens are B fragilis, peptostreptococci, and Clostridia. In one study, 808 patients with polymicrobial infection of the peritoneal cavity or nonvisceral soft tissues were candidates for treatment with 1 of 2 antibiotic regimens. Of the isolated anaerobic organisms, E coli and Bacteroides sp were the most common.

**Female Genital Tract Infections**

In pelvic inflammatory disease, the major isolates are Prevotella bivia, Prevotella disiens, Bacteroides spp, and peptostreptococcus.

**Treatment of Anaerobic Infections**

Table 6 lists the classes of antibiotics and their activity against anaerobes. Of note, 4 antibiotics are always active against anaerobic bacteria: metronidazole, imipenem, and a β-lactam/β-lactamase inhibitor. There are only about 6 recorded isolates resistant to metronidazole, but they are clearly very rare. The macrolides/ketolides are active against most anaerobes but not fusobacteria. Tetracycline is quite variable, and vancomycin and linezolid are active against gram-positive anaerobes.

With regard to resistance, Snydman et al measured the activity of clinical isolates of B fragilis from 1990 to 1996 for 4000 strains obtained from 8 different centers. The results showed an increase in resistance to cefotaxin, clindamycin, and piperacillin. A more recent survey by Aldridge et al shows that 100% of 3 most common pathogens (B fragilis, Prevotella, and peptostreptococcus) were uniformly sensitive to piperacillin/tazobactam, imipenem, and metronidazole. Also, 100% of Prevotella and peptostreptococci but only 93% of B fragilis were sensitive to cefotaxin. Lower susceptibility rates were noted for penicillin G, ciprofloxacin, and clindamycin. The results highlight the variability in resistance patterns among anaerobes, which may be both regional and temporal. The results seem to be sufficiently predictable so that most laboratories do not perform these tests.
CONCLUSION

Anaerobic bacterial microbiology went through a substantial evolution of change so that diagnosis and treatment are now standardized to recognize these microbes and treat them without assistance from the laboratory.

REFERENCES