Reemergence of Anaerobic Bacteremia

Britta Lassmann,† Daniel R. Gustafson,‡ Christina M. Wood,§ and Jon E. Rosenblatt‡
Departments of †Internal Medicine and ‡Clinical Microbiology and §Division of Biostatistics, Mayo Clinic, Rochester, Minnesota

(See the editorial commentary by Hecht on pages 901–3)

Background. During 1974–1988, the incidence of anaerobic bacteremia at the Mayo Clinic (Rochester, MN) decreased. This trend occurred nationally, prompting calls for discontinuation of routine anaerobic blood cultures. However, recently, the sites of anaerobic infection have been shown not to be as predictable as once thought, and since 1993, the incidence of anaerobic bacteremia has increased significantly in our medical center.

Methods. Records from the Mayo Clinic Division of Clinical Microbiology were used to tabulate the number of cases of anaerobic bacteremia in patients at the clinic for the 12-year period from 1993 through 2004. Medical records for patients with anaerobic bacteremia were reviewed from the periods of 1993–1994 and 2004 to identify differences between these 2 patient populations with different rates of bacteremia.

Results. The mean incidence of anaerobic bacteremias increased from 53 cases per year during 1993–1996 to 75 cases per year during 1997–2000 to 91 cases per year during 2001–2004 (an overall increase of 74%). The total number of cases of anaerobic bacteremia per 100,000 patient-days increased by 74% (P < .001). The number of anaerobic blood cultures per 1000 cultures performed increased by 30% (P = .002). Organisms from the Bacteroides fragilis group, other species of Bacteroides, and Clostridium species were most commonly isolated.

Conclusions. Anaerobic bacteremia has reemerged as a significant clinical problem. Although there are probably multiple reasons for this change, the increasing number of patients with complex underlying diseases makes the clinical context for anaerobic infections less predictable than it once was. Anaerobic blood cultures should be routinely performed in medical centers with a patient population similar to ours.

Anaerobic bacteria are important pathogens in many different infections. Anaerobic bacteremia has been most frequently related to an abdominal infection source (in 50%–70% of cases), pelvic infections (in 5%–20% of cases), and skin and soft-tissue infections (in 5%–20% of cases). Anaerobes have accounted for 0.5%–12% of all cases of bacteremia, depending on the institution [1–8]. The Bacteroides fragilis group, Clostridium species, and Peptostreptococcus species are the most frequent anaerobic blood culture isolates. Organisms of the B. fragilis group have been found in up to 65% of cases of anaerobic bacteremia [2, 9]. Anaerobic bacteremia is infrequent in children, and older persons are reportedly at higher risk; mortality remains high. Studies from the Mayo Clinic (Rochester, MN) in the early 1970s reported the frequency of obligate anaerobes in positive blood culture results to be 11.2%–27%. At the Mayo Clinic, the number of anaerobic bacteremia cases decreased by 45% during 1974–1988, although the number of aerobic bacteremia cases increased [10]. A decrease in the incidence of anaerobic bacteremia was also reported in multiple other studies [2, 11–13]. The decrease in anaerobic bacteremia cases was explained by the routine use of bowel preparations prior to abdominal surgery and increased awareness of the appropriate use of antimicrobial agents with activity against anaerobes. Because of this decrease in the incidence of anaerobic bacteremia, selective rather than routine use of an anaerobic bottle for culturing blood samples has been proposed in the medical literature. Two separate authors [14, 15] suggested that it was not important to recognize anaerobic bacteremia microbiologically. They suggested that patients could be identified clinically as having probable anaerobic infection with a high degree of predictability and should be treated empirically without the need for culture confirmation. At the Mayo Clinic, we have always used aerobic and anaerobic blood culture bottles routinely.

In recent years, there has been evidence of an increase in anaerobic infections. Cockerill et al. [8] reported...
that, during 1984–1992, there was an actual increase in the incidence of anaerobic bacteremia at the Mayo Clinic; however, no statistical significance was shown. In a 12-year study at an Australian general hospital, Riley and Arvavena [16] found a 200% increase in the incidence of anaerobic bacteremia, with *Fusobacterium* species and anaerobic cocci being more frequently identified. Other investigators have also reported increases in the incidence of anaerobic bacteremia, particularly during the late 1980s and early 1990s [17–19]. Reasons for this increase were unclear. Speculations ranged from the use of improved culture media and methods to changes in the demographic characteristics of patients and underlying diseases. At the Mayo Clinic, we also observed an increase in the absolute number of cases of anaerobic bacteremia during recent years. To verify that this was a statistically significant increase, we conducted a retrospective study of the incidence of anaerobic bacteremia during the 12-year period from 1993 through 2004. We also conducted a review of patients’ medical records in an attempt to define clinical parameters that might be associated with the increase.

**METHODS**

The Mayo Clinic Microbiology Laboratory services 2 teaching hospitals with a total of 1600 beds. Blood culture samples are obtained by a team of phlebotomists trained and managed by the laboratory staff. All blood culture specimens are processed in the laboratory within 4 h after collection. For the first blood culture ordered during a 24-h period, 2 separate venipunctures are routinely performed. The recommended volume of blood for culture is 20 mL. The blood sample is equally distributed to the anaerobic and aerobic bottles and is incubated for 5 days. From 1993 to 1996, Isolator tubes (Wampole Laboratories) and vented and nonvented Septi-Chek TSB bottles (Becton Dickinson Diagnostic Instrument Systems) were used for recovery of bacteria, mycobacteria, and fungi from blood samples. From 1996 to 2000, Isolator tubes and anaerobic and aerobic Bactec bottles (Becton Dickinson Diagnostic Instrument Systems) were used. From 2000 to present, 2 Bactec aerobic bottles and 1 Bactec anaerobic bottle have been used routinely, and special fungal/mycobacterial bottles are added if requested by a physician. Studies have documented that the recovery of anaerobic bacteria is comparable using these different blood culture systems [8, 20].

Computer-generated and hand-counted records from the Mayo Clinic Clinical Microbiology Laboratory were reviewed to tabulate the number of cases of anaerobic bacteremia at the clinic during the 12-year period from 1993 through 2004. Cases of bacteremia were counted once per patient, unless ≥14 days elapsed between positive blood culture results or the subsequent isolation revealed a different organism. Positive blood culture results for *Propionibacteria* species, *Actinomyces* species, and *Lactobacillus* species were not included in the tabulations. Only bacteremia cases that occurred in patients at the Mayo Clinic were included in this study. Individual episodes of bacteremia and positive blood culture results are represented in absolute numbers and percentages.

The medical records of all patients who had provided research-use permission in 1993, 1994, and 2004 were reviewed to identify clinical conditions that might have had a significant association with anaerobic bacteremia. Underlying diseases, immune status, prior surgery, and, if possible, source of bacteremia were tabulated. An immunocompromised state was defined as immunosuppression due to high doses of corticosteroid therapy or other immunosuppressive drugs, anticancer chemotherapy, or the presence of leukopenia or neutropenia. Patients were classified as having underlying malignancy if they had advanced metastatic disease or were undergoing chemotherapy or radiation therapy at the time of the occurrence of bacteremia. Many of the patients receiving these therapies were also classified as immunocompromised. Prior surgery was defined as surgery within 10 days before the positive blood culture result.

**Statistical methods.** Descriptive information about patients with bacteremia was reported as means (±SDs) for continuous variables or percentages for categorical variables. Age of patients presenting with anaerobic bacteremia during 1993–1994 versus 2004 was compared using a Wilcoxon rank sum test. Similar types of malignancies were compared for the 2 periods. The distribution of conditions in the same time periods were compared using Fisher’s exact test. Rates of bacteremia per patient-days and rates of positive blood cultures for anaerobes per total number of blood cultures performed were calculated to ensure that any changes observed were not simply secondary to changes in the number of patients seen or blood cultures performed during 1993–2004. Because the collected data were in the form of counts, the SEs of event rates were calculated using a cumulative Poisson distribution. The rates of bacteremia during the 2 time periods (1993–1996 and 2001–2004) were compared using a normal approximation to the Poisson distribution. An α level of 0.05 was used; *P* <.05 was considered to be statistically significant.

**RESULTS**

The mean incidence of anaerobic bacteremia increased from 53 cases per year during 1993–1996 to 75 cases per year during 1997–2000 to 91 cases per year during 2001–2004 (an overall increase of 74%, compared with baseline years) (figure 1). During the same period, the proportion of aerobic bacteremia at our institution decreased (table 1). The number of cases of anaerobic bacteremia per 100,000 patient-days increased by 74% (*P* <.001). The number of positive anaerobic blood culture
Figure 1. Occurrence of cases of anaerobic bacteremia, per year, at the Mayo Clinic (Rochester, MN).

Results per 1000 cultures performed during 1993–2004 increased by 30% \( (P = .002) \) (table 2).

Organisms that cause anaerobic bacteremia are shown in table 3. Organisms from the \textit{B. fragilis} group, other species of \textit{Bacteroides}, and \textit{Clostridium} species were most commonly isolated. Bacteremia caused by gram-positive coccii increased relatively in frequency during the 12-year period. The mean ages (± SD) of patients presenting with anaerobic bacteremias did not differ significantly between the 2 periods (60 ± 19 years during 1993–1996 vs. 61 ± 19 years during 2001–2004; \( P = .16 \)). Two percent of the patients were <16 years of age. Fifty-three percent of the patients were male.

Ninety-eight medical records from 2004 and 105 records from the period during 1993–1994 were reviewed. The demographic characteristics of patients are summarized in table 4; there was not an overall statistically significant difference in underlying patient characteristics \( (P = .52) \). There was a higher rate of immunosuppressed patients in 2004 than during 1993–1994, but no significant difference was shown \( (30\% \text{ vs. } 26\%, \ P = .64) \). There was a trend towards an increase in the proportion of patients with anaerobic bacteremia who had undergone bone marrow transplantation in 2004, compared with that during 1993–1994 \( (6\% \text{ vs. } 1\%, \ P = .058) \). The proportion of patients who had undergone surgery prior to the occurrence of anaerobic bacteremia was similar \( (16\% \text{ vs. } 18\% \text{ during 1993–1994}; \ P = .85) \). There was a greater proportion of patients with anaerobic bacteremia with underlying malignancies in 2004 than during 1993–1994; however, no statistically significant difference was shown \( (46\% \text{ vs. } 39\%, \ P = .39) \). Hematologic malignancies were most common during both periods, followed by gastrointestinal, gynecological, and urogenital malignancies (table 5); however, there was not an overall statistically significant difference in underlying malignancies \( (P = .34) \). The increase in the proportion of peptostreptococcal infections from the period during 1993–1994 to 2004 was not statistically significant \( (from 5\% \text{ to } 15\%; \ P = .065) \).

**DISCUSSION**

At the Mayo Clinic, the mean incidence of anaerobic bacteremia increased from 53 cases per year during 1993–1996 to 75 cases per year during 1997–2000 to 91 cases per year during 2001–2004 \( (an \text{ overall increase of } 74\%) \). The rate of anaerobic bacteremia per 100,000 patient-days also increased from 16.0% to 23.9% to 27.8%, respectively, during the same periods. In addition, rates of positive blood culture results for anaerobes per 1000 blood cultures performed increased from 1.68% to 2.02% to 2.17%. This standardizing of rates ensured that the changes observed were real increases and not simply secondary to changes in the number of patients seen at our institution or an increase in the total number of blood cultures performed over time.

We do need to recognize that methods of performing blood cultures at our institution changed during the study period. In 1996, the blood culture detection system used at the Mayo Clinic was changed from Septi-Chek bottles to aerobic and anaerobic Bactec bottles. Studies have documented that the recovery of anaerobic bacteria is comparable using these different blood culture systems \( [8, 20] \). Moreover, if the frequency of anaerobic bacteremia was related to changes in culture media or detection methods, we would expect to see a sudden increase

Table 1. Anaerobes and aerobes as percentage of all organisms causing bacteremia, per year, at the Mayo Clinic (Rochester, MN).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobes</td>
<td></td>
<td>5.4</td>
<td>7.6</td>
<td>6.5</td>
<td>6.2</td>
<td>7.8</td>
<td>8.3</td>
<td>7.2</td>
<td>7.5</td>
<td>9.2</td>
<td>8.5</td>
<td>8.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Aerobes</td>
<td>* Including all organisms other than obligate anaerobes.</td>
<td>94.6</td>
<td>92.4</td>
<td>93.5</td>
<td>93.8</td>
<td>92.2</td>
<td>91.7</td>
<td>92.8</td>
<td>92.5</td>
<td>90.8</td>
<td>91.5</td>
<td>92.0</td>
<td>89.6</td>
</tr>
</tbody>
</table>
Table 2. Number of cases of anaerobic bacteremia per 100,000 patient-days and positive anaerobic blood culture results per 1000 blood cultures performed at the Mayo Clinic (Rochester, MN).

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of cases of anaerobic bacteremia per 100,000 patient-days</th>
<th>No. of positive anaerobic blood culture results per 1000 blood cultures performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993–1996</td>
<td>16.0</td>
<td>1.68</td>
</tr>
<tr>
<td>1997–2000</td>
<td>23.9</td>
<td>2.02</td>
</tr>
<tr>
<td>2001–2004</td>
<td>27.8</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Table 3. Types of anaerobic bacteremia at the Mayo Clinic (Rochester, MN), as percentages of the total number of cases of anaerobic bacteremia per year.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides fragilis group</td>
<td>34.8</td>
<td>42.9</td>
<td>37.3</td>
<td>32.9</td>
<td>31.3</td>
<td>39.1</td>
<td>32.6</td>
<td>31.5</td>
<td>39.0</td>
<td>25.8</td>
<td>38.9</td>
<td>38.8</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>45.7</td>
<td>24.3</td>
<td>28.8</td>
<td>30.1</td>
<td>26.3</td>
<td>14.9</td>
<td>23.3</td>
<td>19.1</td>
<td>22.9</td>
<td>16.1</td>
<td>16.8</td>
<td>20.7</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>4.3</td>
<td>5.7</td>
<td>3.4</td>
<td>9.6</td>
<td>8.8</td>
<td>10.3</td>
<td>14.0</td>
<td>13.5</td>
<td>12.7</td>
<td>16.1</td>
<td>20.0</td>
<td>14.7</td>
</tr>
<tr>
<td>Non–spore forming gram-positive bacteria</td>
<td>0</td>
<td>4.3</td>
<td>18.6</td>
<td>5.5</td>
<td>11.3</td>
<td>11.5</td>
<td>7.0</td>
<td>6.7</td>
<td>10.2</td>
<td>7.5</td>
<td>8.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Other Bacteroides species and anaerobic gram-negative bacteria</td>
<td>13.0</td>
<td>18.6</td>
<td>8.5</td>
<td>17.8</td>
<td>15.0</td>
<td>18.4</td>
<td>18.6</td>
<td>21.3</td>
<td>11.9</td>
<td>24.7</td>
<td>11.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Prevotella and Porphyromonas species</td>
<td>2.2</td>
<td>4.2</td>
<td>3.4</td>
<td>4.1</td>
<td>7.3</td>
<td>5.8</td>
<td>4.5</td>
<td>7.9</td>
<td>3.3</td>
<td>9.8</td>
<td>4.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Other authors [22] have also noted an increased risk of anaerobic bacteremia among patients with hematologic disease. Brook and Frazier [23] showed the importance of obtaining specimens adequate for the recovery of both aerobic and anaerobic bacteria in patients with underlying malignancy and infection. In 2004, 46% of patients in our study had underlying active malignant diseases, most of which were hematologic or gastrointestinal malignancies. We observed an increase in genitourinary malignancies among patients with anaerobic bacteremia in 2004. Malnutrition and immunosuppression, often seen in patients with advanced malignant processes, can further contribute to the development of systemic infection. Immunosuppression is also reported to be associated with anaerobic bacteremia. Lark et al. [24] reported an increase in the number of anaerobic bloodstream infections among patients who underwent bone marrow transplantation at their institution during 1995–1998. In our study, we also noted a trend towards an increase in the proportion of patients with anaerobic bacteremia who had undergone bone marrow transplantation in 2004, compared with that during 1993–1994.

The proportion of patients who had surgery prior to the occurrence of anaerobic bacteremia was similar in the 2 periods reviewed in our study. At the Mayo Clinic, prophylactic antibiotic therapy given prior to dental, upper respiratory tract, genitourinary, and gastrointestinal procedures, along with preoperative cleansing of the bowel, have been standard of care since the 1970s. Thus, although the kinds of surgical procedures performed may have changed during the study period, measures to prevent surgically related infections have been in place for many years. Another factor to consider for the increase in the incidence of anaerobic bacteremia is the increase in the number of elderly patients. Although this was not shown in our study, age may still be a factor influencing the incidence of anaerobic bacteremia in hospitals. A predilection for anaerobic bloodstream infections in elderly patients was shown previously [25].

The spectrum of causative organisms reported at the Mayo Clinic during the 12-year study period was similar to that re-
ported elsewhere [1, 2, 5, 26]. Bacteroides species were the most common isolates, followed by Clostridium and Peptostreptococcus species. There was an increase in the proportion of peptostreptococcal infections during the 12-year period (table 3), although no statistical significance was shown. Predisposing factors to peptostreptococcal bacteremia include malignancy, immunosuppression, and recent gastrointestinal or gynecological surgery [7, 27, 28]. Brook and Frazier [23] reported that Peptostreptococcus species is the second most common anaerobic isolate in patients with underlying malignancy. The importance of identifying infection caused by Peptostreptococcus species is underlined by unpublished data from the Mayo Clinic that show increasing resistance of Peptostreptococcus species to metronidazole. Antimicrobial susceptibilities of anaerobes are generally thought to be more predictable than those of other bacteria. Several antimicrobial agents are active against the most clinically significant anaerobes (β-lactam/β-lactamase–inhibitor combinations and carbapenems). However, the increasing resistance of anaerobes to some agents has been observed [29–31], making their susceptibility patterns less predictable. Recognition of specific anaerobes responsible for bloodstream infections and familiarity with their susceptibility patterns is, therefore, of increasing importance.

Increased awareness of the importance of anaerobes and enhanced recognition of the types of clinical infection caused by these organisms, along with appropriate prophylaxis and treatment, were postulated as reasons that explain the decrease in the incidence of anaerobic bacteremia during 1974–1988 [10]. In a review of 14 studies published during 1956–1974, Finegold [32] found that the gastrointestinal tract accounted for 49% of anaerobic bacteremia cases, and the female genital tract was the source of 20% of cases of anaerobic bloodstream infection. Sources were unknown for only 6% of cases. Lombardi et al. [2] showed that 72% of patients with anaerobic bloodstream infection at the University of Michigan Hospitals during 1987–1988 had the genitourinary and gastrointestinal tracts as sources of infection. In a study conducted by Morris et al. [14] at Duke University Medical Center from August 1989 to February 1991, investigators indicated that the source of infection was clinically obvious in 84% of patients with anaerobic bacteremia. They concluded that because the types of infection causing anaerobic bacteremia were generally predictable, anaerobic blood cultures should be performed selectively. Other investigators have echoed this recommendation, partly because the rates of anaerobic bacteremia in their studies were quite low [2, 11, 12, 15].

On the other hand, recognition of the “typical” clinical contexts for anaerobic bacteremia at our institution seems to be less predictable than it once was. Our data showed that 38% of patients with anaerobic bacteremia in 2004 had sources other than the genitourinary and gastrointestinal tracts. Internal review of unpublished data from the Mayo Clinic during 1995–1996 showed that, in 34.3% of patients, anaerobes would not have been suspected as the cause of bacteremia on the basis of “typical” clinical predictors. Sources of anaerobic bacteremia are now more varied than previously, especially among immunosuppressed patients and patients with complex underlying disease.

In conclusion, this study demonstrates an increase in the frequency of isolation of anaerobic bacteria from blood cultures at our institution. This increase, along with the emergent resistance to antimicrobial agents and diminishing ability to reliably predict sources of infection, should justify the routine use of anaerobic blood culture bottles in medical centers with a similar clinical practice to ours.

### Acknowledgments

**Potential conflicts of interest.** All authors: no conflicts.

### References