CLOSTRIDIAL SEPTICEMIA IN AN URBAN HOSPITAL

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The records of 56 patients at an urban hospital who had positive blood cultures for clostridia were reviewed. Each patient was classified as immunologically normal or immunosuppressed. Data were collected on clinical history, type of clostridial bacteremia, physical and laboratory determinants of infection, therapeutic intervention, clinical course and outcome.

Of the 56 patients, 22 were determined to be immunosuppressed. Among all 56 patients, 28 had a malignancy, usually gastrointestinal or hematologic in origin. Fever, leukocytosis and abdominal pain were common in both groups. Clotridial bacteremia almost always heralded clotridial sepsis. A gastrointestinal source of infection, particularly carcinoma of the colon or rectum or enterocolitis, was evident or presumed in 35 of the 56 patients. Clotidium perfringens was the most frequently isolated microorganism, but C. septicum was associated with more complications and a higher mortality rate. Septic complications and mortality were higher among the patients with immunosuppression.

Clostridial sepsis is a rare condition in urban hospitals, but its associated mortality is exceedingly high despite many advances in antibiotic therapy and other aspects of critical care management. In a recent study of patients on the surgical service, clostridia was found in only 22 of 1,708 positive blood cultures, but the patient mortality rate was 40 per cent (1). Findings at presentations are often vague and the diagnosis often is not established until autopsy. Few patients present with the usual findings of gas gangrene or hemolysis (2-4). To address these issues, the records of all patients with positive clostridial blood cultures treated at the New York Hospital-Cornell Medical Center during a period of 20 years were examined.

MATERIALS AND METHODS

The bacteriologic records of the hospital from 1970 through 1989 were reviewed to identify all patients with at least one blood culture positive for a clostridial organism other than Clotidium difficile. Microbiologic techniques have been described in a previous study (1).

Positive blood cultures were identified in 59 patients, of whom 56 had hospital records available for review. Data were collected on history, date of identification of clotridial bacteremia, associated bacteremia from nonclostridial organisms, physical and laboratory determinants before and during clotridial bacteremia, therapeutic interventions, focus of infection, complications, clinical course and outcome.

One of the investigators, unaware of patient outcome, classified patients as immunologically normal or immunosuppressed. The criteria for immunosuppression were chemotherapy for carcinoma within three weeks before onset of bacteremia; steroid administration at the time of diagnosis of bacteremia; acquired immunodeficiency syndrome (AIDS) or the combination of anemia, thrombocytopenia and either neutropenia or previously demonstrated inability to mount an elevated white blood cell count in response to infection. Age, diabetes, presence of neoplasia or anemia alone were not criteria for immunosuppression.

Data were entered in a dBase III Plus database program. Statistical analysis was performed with EPI INFO (USD Inc.) software using chi-square or Fisher's exact tests as appropriate.

RESULTS

Demographic data. Of the 56 patients with clotridial bacteremia, 32 were males and 24 were females. The mean age was 53 years, ranging from 17 months to 85 years. Twenty-two patients were deemed immunosuppressed (two had AIDS). Only four of the 22 immunosuppressed patients were 70 years of age or older, compared with 14 of the remaining 34 patients (p=0.051). The immunosuppressed and remaining patients were similar with regard to gender and race. Clotidium perfringens, the most frequently isolated species, was found in 26 patients, C. septicum in 11 and C. ramosum in six (Tables 1 and II).

Pathogenesis. Based on clinical and operative findings or findings at autopsy, the gastrointes-
TABLE I—SOURCE OF SEPTICEMIA

<table>
<thead>
<tr>
<th>Location</th>
<th>Clostridium perfringens</th>
<th>Other Clostridium</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right colon</td>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>1</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Left colon</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intestine, nonspecified</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Uterine/vaginal trauma</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Source unknown</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>39</td>
<td>65</td>
</tr>
</tbody>
</table>

Table 1: Right colon, transverse colon, and total. Small intestine includes the nonspecified intestine. Gallbladder, uterine/vaginal trauma, and source unknown are also included in the total.

The table shows the number of patients with septicemia due to different sources. The total number of patients is 56, with 26 patients having C. perfringens, 11 having C. septicum, and 39 having other Clostridium species.

The character of mixed infections also indicated that most instances of Clostridium bacteremia had a gastrointestinal source. Eighteen of the 56 patients also had positive blood cultures for non-Clostridial microorganisms, most of which were normal intestinal flora, including Bacteroides species, Escherichia coli, Klebsiella species, Streptococcus bovis and Enterococcus faecalis.

Only 4 of 56 patients had Clostridial sepsis arising from a nongastrointestinal source. The organism in all four instances was C. perfringens. The sources were the uterus, vagina, thermal trauma and soft tissue trauma, respectively (Table I).

Although 22 patients were classified as immunosuppressed, many of the remaining 34 patients also had evidence for diminished host resistance (Table III). Eleven of the patients who were non-immunosuppressed had locally advanced carcinoma. Although all patients who were immunosuppressed were anemic (hemoglobin<14 grams per day in men and <12 grams per day in women), 24 of the remaining patients also were anemic. Among the 34 patients who were non-immunosuppressed, seven had diabetes mellitus and 14 were more than 70 years of age, including three who were more than 80 years old.

Clinical findings: Clinical findings were assessed 24 hours before, and at the time of the positive blood culture (Table IV). Data collected 24 hours before the venesection of the positive blood culture were available for only 30 patients. At the time, clinical findings were nonspecific systemic infection with chills, fever and tachycardia, with...
commonly, additional abdominal pain. Only two patients had soft tissue crepitance.

Similarly, at the time of the positive blood culture, the clinical findings were predominantly of severe but nonspecific systemic infection, usually with abdominal pain. With one exception, all other patients had one or more findings of clinical sepsis, although attribution to clostridia was not always possible. Overt findings of classical gas gangrene were uncommon. Crepitance was evident in six patients and hemolysis in only two. Differences between the immunosuppressed and the remaining group in the clinical expression of sepsis were limited.

Later, during the hospitalization period, more patients who were immunosuppressed had septic complications, especially anuria (p=0.01) (Table V). Approximately 40 per cent of the patients had a metabolic acidosis or disseminated intravascular coagulopathy (DIC). Hemolysis was found in only two patients.

Bacteremia versus septicemia. Almost all patients who had clostridial bacteremia were found to have either definite findings of clostridial sepsis or a sufficient probability of clostridial sepsis, obscured by nonspecific findings of infection or blunted by immunosuppression, so as to merit specific treatment. Among the 16 patients who were nonimmunosuppressed with C. perfringens bacteremia, 12 had clostridial sepsis. Of the remaining four patients, two had thermal trauma. Both had fever and tachycardia. One patient also had positive blood cultures for Serratia and Klebsiella species and the other responded after fascial release of a compartment syndrome. The remaining two patients were elderly and had diabetes. One had bleeding of the colon, fever and abdominal pain from a presumed localized perforation because of diverticulitis of the colon and responded to antibiotics alone. The other had fever, leukocytosis and a borderline DIC in association with C. perfringens bacteremia and also responded to antibiotics alone.

Of the six patients with a blood culture positive for C. ramosum, five were regarded as having clostridial sepsis. One patient who had a subarachnoid hemorrhage had leukocytosis but no fever or other clinical findings at the time of positive culture and is presumed to have had bacteremia only.

Of the six patients with positive blood cultures for other defined clostridial species, two were regarded as having bacteremia alone. One patient, who had a C. sardinius culture had anemia, splenomegaly, fever and a stool culture that was positive for salmonella. The other patient, with alcoholic hepatitis and pancreatitis, had a blood culture of C. tertium associated with fever, abdominal pain and tenderness, guaiac positive stools and leukocytosis.

Of six patients with blood cultures positive for unspecified clostridia, all were deemed septic from clostridia. Difficulty in decision making was exemplified by one patient with advanced carcinoma of the sigmoid colon and a sigmoid-vesical fistula, fever, marked leukocytosis and coagulopathy who responded to antibiotics but later died from progression of malignant disease.

Treatment. Among all 56 patients, 36 received only antibiotic therapy, initiated for 32 patients...
whereas among "normal" patients, nine of those with a strangulated ventral hernia with small bowel obstruction were administered to 12 patients within 12 hours of culture. Of the six patients who died after both antibiotic and operative management, three had soft tissue crepitance and myonecrosis. Only one of three patients had operative intervention within 24 hours after appearance of soft tissue invasion.

To assess treatment efficacy without confounding by immunosuppression and *C. septicum* infection, mortality in the 16 patients who were nonimmunosuppressed and had *C. perfringens* sepsis was analyzed. Of the 16 patients, three had advanced carcinoma. Broad spectrum antibiotics were administered to 12 patients within 12 hours of a positive blood culture and to the remainder within 24 hours. Ten patients underwent operative intervention. Two of the 16 patients died. In one instance, death was attributed to advanced metastatic carcinoma of the stomach. The only "normal" patient who died from *C. perfringens* sepsis was a woman who was 83 years old and who had a strangulated ventral hernia with small intestinal perforation and peritonitis. She was treated promptly with broad spectrum antibiotics and early operative intervention, but died less than 24 hours after admission.

**Outcome.** Among all 56 patients, there were 23 deaths (a mortality rate of 41 per cent), which is similar to that reported for our surgical service alone (1) (Table II). Among the patients regarded as immunosuppressed, 14 of 22 died, whereas among the "normal" patients, nine of 34 died during the hospitalization period. However, 11 of the 23 patients who died while in the hospital were found to have died, not from clostridial sepsis, but from their underlying disease, namely advanced lymphoma in two patients, metastatic sigmoid carcinoma in two and carcinoma of the breast, carcinoma of the gastrointestinal tract, carcinoma of the ovaries, carcinoma of the uterus, AIDS, hepatic failure and arrhythmia in one each. Thus, the mortality rate from clostridial sepsis was 21 per cent (12 of 56) overall, with 45 per cent (ten of 22) among those regarded as immunosuppressed, and only 6 per cent (two of 34) among the remaining patients. The mortality rate for those treated with antibiotics alone (22 per cent) was similar to that for the patients who received combination therapy (21 per cent).

Mortality was associated with the clostridial species (Table II). The mortality rate from sepsis with *C. septicum* (7 of 11) was significantly higher (p=0.003) than that with *C. perfringens* (three of 26) or other species (two of 19).

Two of five "normal" patients and five of six patients who were immunosuppressed with *C. septicum* died from sepsis. Morbidity also was greater with *C. septicum* than with other species (Table VI). Patients with sepsis from *C. septicum* had more myonecrosis (p=0.02) than patients with sepsis from *C. perfringens* and seemed more likely to have DIC and metabolic acidosis.

**DISCUSSION**

In the urban hospital population of the current study, clostridial bacteremia most often had a gastrointestinal source, either directly from gastrointestinal neoplasia or indirectly from mucosal translocation in a setting of weakened host resistance. Clostridial bacteremia was almost always associated with findings of sepsis and merited prompt investigation and treatment.

Few patients had a classical presentation. More often, onset was insidious. Sepsis from *C. septicum* was less frequent than that from *C. perfringens*, but had a higher risk of mortality and was more frequently associated with carcinoma of the gastrointestinal tract.

Most of the patients with clostridial sepsis had a background of weakened host resistance. Immunologic impairment has been associated with a greater risk for clostridial infection and a higher mortality rate, particularly for *C. septicum* (2, 4–8). The studies also suggested the importance of immune compromise in sepsis from *C. perfringens* and other clostridial species. Our criteria for immunosuppression (chemotherapy, steroids, hematopoietic suppression) underestimated the importance of immunologic impairment in clostridial infection. Older age, advanced malignancy, malnutrition and anemia were found regularly among these patients. In addition, diabetes mellitus, found in 21 per cent of the patients, and atherosclerosis favor ischemia, and are thought to contribute to pathogenesis of infection (5–8).

The association between *C. septicum* sepsis and...
gastrointestinal or hematologic malignancy have been described by others (1, 2, 4, 5, 7–9). In the current series, sepsis frequently originated with *C. perfringens* from the gastrointestinal tract, particularly the left colon and in enterocolitis. Bacteremia or sepsis from other clostridial species also commonly arose from the gastrointestinal tract.

To a considerable extent, the clinical expression of clostridial sepsis found in the surgical service differed from that found in the medical service. Origin tended to a recognizable and correctable focus, such as cholangitis, abscess or trauma in the surgical service. Onset appeared more insidious in the medical service, typically in a profoundly ill patient undergoing immunosuppressive treatment for advanced neoplasia. Among such patients, the pathogenesis of clostridial sepsis may be associated with bacterial translocation and necrotizing enterocolitis.

Direct breakdown of the gastrointestinal mucosa has been seen in patients with clostridial infection and no other apparent source (2, 6). Bacterial translocation has been found in animals in the setting of host immunosuppression or exposure to severe stress (10–12). Mice that were free of germs and athymic had spontaneous translocation of indigenous gastrointestinal flora, whereas mice with intact T cell mediated immunity did not. Malnutrition, associated with reduction of fiber intake, may contribute to loss of mucosal barrier function (13). In the patient who is immunosuppressed and has carcinoma, erosions of the gastrointestinal mucosal from leukemic infiltration, cytotoxic chemotherapy, or hemorrhage from thrombocytopenia also may promote translocation (14).

The necrotic environment of tumor in the compromised intestine, with anaerobic glycolysis and acidic milieu, may favor germination of clostridial spores (9). Under the circumstances, the organism may not need to colonize the gastrointestinal tract but merely to be present. Intravenous injection of *C. tetani* spores in mice that had tumors resulted in growth of the organism with production of lethal toxin levels, but not in healthy mice (15). Spores injected into tissue that was nonmalignant and necrotic also germinated, but did not affect neighboring normal tissue (16).

Endotoxemia, which occurs commonly in patients who are immunocompromised and alters gastrointestinal mucosal integrity, probably contributes further to pathophysiologic translocation. Endotoxin has promoted a dose dependent translocation of indigenous flora in mice (10). Endotoxemia is mediated by a complex cascade of endogenous cytokines and counter regulatory hormones, including splanchnic production necrosis of the tumor factor (17). A gastrointestinal origin of sepsis and the role of endotoxemia were supported further in the current study by the finding of other gram-negative enteric microorganisms occurring as mixed bacteremias with clostridia.

In the current study, patients who were and were not nonimmunosuppressed, did not differ notably in presenting pattern. In both groups, most patients presented with fever, leukocytosis and abdominal pain. Findings described in association with clostridial infection, such as pulse-temperature dissociation, intravascular hemolysis and crepitance, were infrequent and contributed little to early diagnosis.

The confounding lethal power of background host disease and immunosuppressive intervention differences in species virulence, variables in treatment decisions and the absence of controls precludes generalizations about the efficacy of treatment. In the nonimmunosuppressed cohort with *C. perfringens* sepsis, antibiotic and operative treatment appeared effective.

When clostridial sepsis is suspected, high dose antibiotic therapy, such as 40 million units of aqueous penicillin given intravenously per day, or of 4 grams of chloramphenicol per day, should be initiated promptly after blood cultures are obtained. Two grams per day of metronidazole and 4.8 grams per day of clindamycin provide alternatives but are not as effective.

Operative intervention requires both recognition of clostridial sepsis and localization of a remedial source of infection. The rarity of clostridial septicemia and its frequently insidious onset lowers the index of suspicion and are obstacles to early and aggressive therapy. Soft tissue pain and swelling, harbingers of fulminant myonecrosis, not only require aggressive local inter-

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clostridia perfringens, n=11</th>
<th>Clostridia perfringens, n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myonecrosis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Anuria</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DIC</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>7</td>
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</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulopathy.
vention, but may herald an occult gastrointestinal malignancy (18, 19).

SUMMARY

The records of 56 patients with blood cultures positive for clostridial species at the New York Hospital were reviewed. The patients were divided into categories of immunocompromised or immunologically normal. Most patients had a gastrointestinal source of infection, for which bacterial translocation and tumor necrosis, particularly in the colon, were important pathogenetic mechanisms. Mortality risk was associated with the specific clostridial organism and with immunosuppression. Among 16 immunologically normal patients with C. perfringens sepsis, only one patient died because of infection. The findings of a patient who is immunosuppressed with clostridial bacteremia, abdominal pain and tenderness and no other apparent source of sepsis, should increase suspicion. A thorough search for localized gastrointestinal pathologic findings, particularly carcinoma of the colon or enterocolitis, should be made. An exploratory laparotomy may be indicated.

REFERENCES