Significance of *Clostridium tertium* Bacteremia in Neutropenic and Nonneutropenic Patients: Review of 32 Cases

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In the nonneutropenic host, bacteremia due to *Clostridium tertium* is rare and of unclear significance. We describe a patient in whom presentation with *Clostridium tertium* bacteremia was the harbinger of Crohn’s disease. In order to understand the significance of *C. tertium* bacteremia in neutropenic and nonneutropenic hosts, we review all 32 cases of *C. tertium* bacteremia that occurred at Duke University Medical Center from 1992 to 1999.

Bacteria of the genus *Clostridium* are a diverse group of gram-positive, spore-forming, anaerobic bacilli found in the soil and the gut of many animal species, including humans [1]. Bacteremia with these organisms is rare [1] and occurs primarily in the setting of intra-abdominal sepsis associated with trauma or surgery [2–4]. It has also been associated with other gastrointestinal disorders, pregnancy, and malignancies [2–4]. Although most reports suggest that bacteremia with either *Clostridium septicum* or *Clostridium perfringens* is a marker for underlying gastrointestinal tract pathology [1, 5], *Clostridium ramosum* [4], *Clostridium sordellii* [6], and *Clostridium tertium* [7, 8] have also been associated with gastrointestinal tract disease.

*C. tertium* distinguishes itself among the clostridia as a non-toxin-producing, aerotolerant species [1, 9]. Initially isolated by Henry [9] from war wounds in 1917, it was not until the first human cases of *C. tertium* bacteremia were reported in 1963 that *C. tertium* was recognized as a human pathogen [10]. Since then, *C. tertium* has been most frequently isolated from blood cultures [2, 7, 11], although it has also been reported to cause spontaneous bacterial peritonitis [12], brain abscess associated with lawn dart trauma [13], nasopharyngeal carcinoma [4], and pneumonia [10, 14]. Importantly, most patients with *C. tertium* bacteremia have been neutropenic without a defined source of infection. In contrast, bacteremia in the nonneutropenic host has only rarely been described, and even when *C. tertium* is isolated in this setting, its significance is often unclear [7, 10].

To our knowledge, we describe the first case of *C. tertium* bacteremia as part of the presenting illness of a nonneutropenic patient with Crohn’s disease. In addition, in an effort to further define the source and significance of *C. tertium* bacteremia, we review all cases of *C. tertium* bacteremia that occurred at Duke University Medical Center from 1992 to 1999.

**Methods.** We reviewed the medical records of all patients for whom blood culture results were positive for *C. tertium* from 1 January 1992 to 31 March 1999. All isolates were identified by the microbiology laboratory at Duke University Medical Center (Durham, NC), a large 1000-bed academic tertiary care center. Charts were reviewed for clinical, demographic, and bacteriologic data, including age, sex, underlying disease, history of chemotherapy, clinical outcome, symptoms, absolute neutrophil count, total WBC count, and the presence of other bacteria isolated from blood specimens obtained at the time *C. tertium* bacteremia was diagnosed. Neutropenia was defined as an absolute neutrophil count <500 cells/µL. Bacteremia was considered polymicrobial if ≥1 organism other than *C. tertium* is isolated in culture of any blood specimen obtained within 24 h of the time *C. tertium* bacteremia was diagnosed. In addition, any relevant radiological or pathological information that was discovered subsequent to the isolation of *C. tertium* was included.

Presumptive identification of *C. tertium* was made if the bacteria were gram-positive, aerotolerant bacilli that formed terminal spores under anaerobic conditions only. Identification was confirmed by using the API 20A anaerobic identification system (bioMérieux Vitek) and, in some instances, by analyzing metabolic products by means of gas-liquid chromatography.

**Case report.** A 28-year-old man presented with midabdominal pain, vomiting, and diarrhea after eating a fried fish sandwich at a fast-food restaurant. His medical history was remarkable for episodes of midabdominal pain after meals. These episodes would often resolve after vomiting. His vital signs at the time of presentation were notable for a temperature
of 37°C, increase in pulse rate from 111 to 136 beats/min, and a decrease in blood pressure from 110/60 to 100/52 mm Hg when he stood up. Physical examination revealed bowel sounds, but his abdomen was diffusely tender to palpation. There were no masses. Stool analysis disclosed no occult blood, but fecal leukocytes were present. His WBC count was 15,200 cells/μL (51% neutrophils and 32% band forms). A plain radiograph of the abdomen showed a small-bowel obstruction with dilated loops of small bowel and no air in the colon.

At the time of admission, the patient was not given anything by mouth and was treated with iv fluids, and a nasogastric tube was placed for decompression. That evening, his temperature rose to 40°C, and he was treated with iv ciprofloxacin and clindamycin. Stool cultures were negative for Salmonella, Shigella, Campylobacter, Yersinia, and Escherichia coli O157:H7, as well as antibodies to Yersinia enterocolitica. Blood culture yielded C. tertium.

Subsequent evaluation included abdominal CT that showed a thickened stenotic segment of distal ileum. Upper gastrointestinal tract radiography and an examination of the small bowel showed thickened loops of ileum and a 25-cm, featureless, dilated distal ileum proximal to a stenotic terminal ileum. The stenotic segment was 2 cm in length and 4 mm in diameter. A biopsy sample was taken from the ileal mucosa, fixed in 10% buffered formalin, and then embedded in paraffin. Hematoxylin-eosin staining revealed changes consistent with Crohn’s disease. Colonoscopy disclosed a stenotic ileocecal valve and a probable fistula arising from the cecum. Histological analysis also showed active colitis consistent with Crohn’s disease.

The patient was treated with mesalamine (800 mg 3 times per day) with resolution of symptoms. Three months after presentation, he remained asymptomatic.

Results. Thirty-two patients were found to have C. tertium bacteremia from 1 January 1992 through 31 March 1999 at Duke University Medical Center. Twenty patients (63%) were male, and the ages of the patients ranged from 16 to 75 years. Twenty-nine patients (91%) were neutropenic, all having received chemotherapy within 9–21 days before the onset of C. tertium bacteremia.

Of the 3 nonneutropenic patients, 1 had end-stage liver disease secondary to chronic alcohol abuse. The second patient had systemic lupus erythematosus, being treated with high doses of steroids, and had a percutaneous gastrostomy tube placed 3 days before isolation of C. tertium. The third patient had Crohn’s disease, as described above.

All 32 patients had oral temperatures >38°C at the time when C. tertium bacteremia was diagnosed. Nineteen patients (59%) had >1 abdominal symptoms: 9 had diarrhea (5 of whom tested positive for Clostridium difficile toxin), 9 had abdominal pain, 5 had nausea, and 1 had constipation.

Of the 13 patients with no abdominal symptoms at the time of C. tertium bacteremia, 7 remained asymptomatic, and 6 had abdominal findings at a subsequent evaluation. These findings included colonic abscess, hepatosplenic candidiasis, retroperitoneal lymphoma, splenic bed abscess following splenectomy, idiopathic abdominal pain and diarrhea, and percutaneous gastrostomy tube placement 3 days before the onset of C. tertium bacteremia.

Cultures of blood specimens from 21 patients were polymicrobial, with enteric flora (table 1). Of these 21 patients, all had neutropenia that had been induced by chemotherapy, and 18 had either abdominal symptoms or a documented intra-abdominal process (e.g., abscess, intra-abdominal mass, or colitis). Monomicrobial bacteremia occurred in all 3 nonneutropenic patients and in 8 neutropenic patients.

Four patients died within 1 week after the isolation of C. tertium. Two of these patients were not neutropenic and had only tertium isolated; 1 had systemic lupus erythematosus, and 1 had end-stage liver disease. The other 2 patients had acute leukemia and multiple organisms in their blood; 1 had necrotizing fasciitis with C. septicum infection, and 1 had small-bowel ischemia with pneumatosis (table 2). The remaining 7 patients who died within 1 month after the isolation of C. tertium had blood cultures negative for C. tertium before death.

Discussion. Three major factors are associated with C. tertium bacteremia: intestinal mucosal injury, neutropenia, and history of exposure to β-lactam antibiotics (particularly third-generation cephalosporins). The connection to intestinal mucosal injury is supported by several observations. First, 25 of our 32 patients with C. tertium bacteremia either had abdominal symptoms at the time that bacteremia was diagnosed or

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of patients</th>
</tr>
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<tbody>
<tr>
<td>Enterococcus species</td>
<td>10</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>6</td>
</tr>
<tr>
<td>Streptococcus bovis</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>1</td>
</tr>
<tr>
<td>Bacillus species</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium septicum</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>1</td>
</tr>
<tr>
<td>Bacteroides species</td>
<td>1</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
</tr>
</tbody>
</table>

* All patients were neutropenic (neutrophil count, <500 cells/μL).
were subsequently found to have an intra-abdominal process, such as an abscess or mass. Second, of the 7 patients who did not have symptoms or known intra-abdominal pathology, all were neutropenic as a result of recent chemotherapy. Because cytotoxic agents are well known to cause significant mucosal disruption of the gastrointestinal tract [15], exposure to these agents most likely potentiated translocation of C. tertium. Third, in the nonneutropenic host, C. tertium bacteremia was associated with intestinal abnormalities. Of our 3 nonneutropenic patients, 1 had severe liver disease and spontaneous bacterial peritonitis, 1 had recent placement of a percutaneous gastrostomy tube, and, as reported in detail, 1 had Crohn's disease. Fourth, 5 of the 32 patients had C. difficile–associated colitis, another cause of mucosal disruption potentiating bacteremia. Finally, 21 of the 32 patients in our series had polymicrobial bacteremia, with enteric flora. Notably, Staphylococcus aureus, an isolate frequently found in blood specimens from hospitalized patients, was not recovered from these patients during the time that they were infected with C. tertium.

The second major factor associated with C. tertium bacteremia is neutropenia. Most patients with C. tertium bacteremia in our series and those described elsewhere in the literature were neutropenic [7, 8, 11, 16–19]. Although exposure to cytotoxic agents produced intestinal injury in most of these patients, it also caused neutropenia. Even though the exact role of neutropenia in the pathogenesis of infection is unclear, one possibility is that it not only potentiates migration of C. tertium into the systemic circulation but also allows it to grow because of a significantly diminished challenge from innate immune responses.

The third factor associated with C. tertium bacteremia is history of exposure to β-lactam antibiotics, particularly third-generation cephalosporins. C. tertium is commonly resistant to many β-lactam antibiotics, clindamycin, and metronidazole but is susceptible to vancomycin, trimethoprim-sulfamethoxazole, and ciprofloxacin [8, 11, 17, 18]. Neutropenic patients, at the time of isolation of C. tertium, had been exposed to third-generation cephalosporins as empirical therapy for neutropenic fever both in our study and in previous reports [7, 8, 11, 17, 18]. Therefore, the selection effect of antibiotics on C. tertium may occur in instances where patients have had prior exposure to β-lactam antibiotics, as is often the case for those under evaluation for neutropenic fever.

Aside from its role as a marker for neutropenia and intestinal mucosal injury, C. tertium bacteremia does cause clinical disease. In our study, all patients with monomicrobial bacteremia had high-grade fever that resolved after initiation of therapy with antibiotics to which C. tertium was susceptible. However, because C. tertium is not histotoxic, lipolytic, or toxin producing [1], mortality related to C. tertium bacteremia treated appropriately appears to be quite low. In one series of 7 patients with C. tertium bacteremia, 6 patients, all of whom had received chemotherapy for hematologic malignancy, survived after appropriate antibiotic therapy [10]. In our series, patients did not die of infection with C. tertium, and in most cases, blood cultures were negative for C. tertium before death. Although the mortality rate within 1 month after isolation of C. tertium from blood was 34%, the mortality rate for the population studied was high because of underlying disease, which, in most cases, was hematologic malignancy. Consistent with reports made elsewhere [47, 81, 2–19], all 4 patients who died within 1 week of isolation of C. tertium had severe underlying disease, polymicrobial cultures, or aggravating factors influencing the outcome (table 2).

In summary, C. tertium bacteremia is a rare cause of fever in both neutropenic and nonneutropenic hosts. The organism is not highly pathogenic, but directed antibiotic therapy for C. tertium bacteremia is indicated and is associated with resolution of fever. Although rare, its presence in any patient should alert the care giver to a disruption in the gastrointestinal tract mucosa. In the absence of an alternative explanation, such as enterocolitis from chemotherapy or recent gastrointestinal tract manipulation, an investigation for other causes of gastrointestinal tract injury should be pursued.

### References


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### Table 2. Characteristics of patients who died within 1 week after isolation of Clostridium tertium from blood.

<table>
<thead>
<tr>
<th>Patient no. (age, y)</th>
<th>Underlying disease</th>
<th>WBC count, $\times 10^9$ cells/L</th>
<th>Complication</th>
<th>Other blood isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (18)</td>
<td>Acute lymphocytic leukemia</td>
<td>0.5</td>
<td>Necrotizing fasciitis</td>
<td>Clostridium septicum</td>
</tr>
<tr>
<td>2 (66)</td>
<td>Acute myelogenous leukemia</td>
<td>0.1</td>
<td>Intestinal bleed, small-bowel ischemia</td>
<td>Enterococcus species, Clostridium species, Candida albicans</td>
</tr>
<tr>
<td>3 (24)</td>
<td>Systemic lupus erythematosus</td>
<td>4.5</td>
<td>Cerebritis, percutaneous endogastric tube</td>
<td>None</td>
</tr>
<tr>
<td>4 (43)</td>
<td>End-stage liver disease</td>
<td>52.1</td>
<td>Spontaneous bacterial peritonitis</td>
<td>None</td>
</tr>
</tbody>
</table>