Bacteremia Due to Clostridium Difficile: Case Report and Review of the Literature

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Abstract

Objective: The purpose of this study is to report a case of C. difficile bacteremia in a Crohn’s disease patient and to review the literature on previously reported cases.

Methods: Searches of MEDLINE and PubMed databases were made.

Results: We report the first case of C. difficile bacteremia in a Crohn’s disease patient. There are 15 other reported cases of C. difficile bacteremia reported in the literature. We found that the majority of patients (10 of 15 patients) had polymicrobial bacteremia and that the overall mortality rate is significant, with 6 of 15 reported patients dying.

Conclusion: In conclusion, we find that C. difficile bacteremia is associated with a significant mortality rate and it would seem prudent to consider aggressive antibiotic therapy.

Keywords: Clostridium difficile, Crohn’s disease, bacteremia

Introduction

Clostridium difficile is the primary cause of pseudomembranous colitis and a major cause of antibiotic-associated diarrhea.¹ In the original report of C. difficile published in 1935 the bacterium was named “the difficult clostridium” because early attempts at isolation were unsuccessful and it grew slowly in culture.³ C. difficile produces an enterotoxin (toxin A) and a cytotoxin (toxin B). Toxin A has been shown to be the cause of diarrhea and pseudomembranous colitis.⁴ C. difficile has rarely been reported to cause extraintestinal disease.¹ The role of toxins A and B in extracolonic manifestations of C. difficile remains unclear. We report a case of C. difficile bacteremia in a Crohn’s disease patient and review the literature on previously reported cases.

Methods

A review of the published literature on C. difficile bacteremia was done using MEDLINE and PubMed databases. Searches were conducted to find articles from 1966–2008. Medical subject headings used to search the databases included C. difficile, including subheadings of bacteremia, extraintestinal disease and Crohn’s disease, as well as a keyword search using “C. difficile bacteremia.” Titles and abstracts of potentially relevant articles were reviewed by a single author.

Case Report

We describe the case of a 50-year-old white male with small bowel Crohn’s disease initially admitted with nausea and abdominal distention secondary to a small bowel obstruction. The patient has a 30 year history of Crohn’s disease involving the jejunum and terminal ileum with multiple proximal small bowel strictures. He has had an appendectomy and back surgery in the past but was never treated surgically for his Crohn’s disease.
He was on maintenance therapy with Azulfidine and Azathioprine. The patient was started on Infliximab in November 2005 after multiple admissions for small bowel obstruction. The patient was changed to Adalimumab in May 2007 for patient convenience and difficulty related to obtaining regular intravenous access. He denied any recent antibiotic use.

Computerized tomography scanning on admission demonstrated a small bowel obstruction with thickened and edematosus small bowel in the right lower quadrant 8–10 cm from the ileocecal valve with a small amount of ascites and no evidence of abscess. A nasogastric tube was placed for decompression and the patient was placed on solumedrol 20 mg intravenous (iv) every eight hours along with aggressive iv hydration and pain management with hydromorphone. The patient initially improved on hospital day number one. On the morning of hospital day number 2, the patient was reported to be febrile to 39.4 °C and tachycardic. The patient was complaining of increased pain and on exam had significantly increased tenderness with absent bowel sounds. At that time, the blood culture drawn on admission was reported as growing *Escherichia coli*, *Enterococcus fecalis* and *Klebsiella oxytoca*. The patient was started on intravenous antibiotics (ampicillin/sulbactam and gentamicin) and taken for an emergent laparotomy. He was found to have a perforation with a free abdominal abscess and a partial small bowel obstruction of the jejunum. He was found to have a perforation with a free abdominal abscess and a partial small bowel obstruction of the jejunum. The patient underwent a small bowel resection with jejunojunostomy and a right hemicolectomy with ileocolonic anastomosis and ileostomy. The pathology revealed a T4N1 poorly differentiated adenocarcinoma of the jejunum. The patient did well clinically post-op however a routine blood culture done for fever on post-op day number one grew *Clostridium difficile*. The patient denied significant diarrhea. Subsequent stool studies sent for *Clostridium difficile* toxins A/B were negative. At that time, the patient had received four days of antibiotics. The patient was maintained on piperacillin-tazobactam. All other follow-up blood cultures were unremarkable. The patient received a total of 21 days of intravenous antibiotics (6 days of ampicillin/sulbactam and gentamicin followed by 15 days of piperacillin-tazobactam). The remainder of his post-op course was unremarkable and he made a full recovery.

**Discussion**

We report the first case of *C. difficile* bacteremia in a Crohn’s disease patient. There are 15 other

| Reference | Sex/Age | Clinical presentation | Stool | Other organisms isolated | Antibiotic exposure | Treatment | Outcome |
|-----------|---------|-----------------------|-------|--------------------------|--------------------|-----------|---------|
| #5        | M/5     | URI                   | NR    | None                     | Penicillin G       | Died      | NR      |
| #6        | M/68    | Cirrhotic admitted    | None  | None                     | None               | Died      | NR      |
| #7        | M/neonate | Necrotic small bowel with<br>bacteremia and septicemia | Ampicillin and<br>kanamycin | Staphylococcus<br>epidermidis (likely procedural contaminant) | Cefuroxime | Oral vancomycin | Died |
| #8        | M/65    | Toe gangrene with septicemia | Ampicillin and<br>kanamycin | Bacteroides fragilis | Metronidazole (iv) | Oral vancomycin | Survived |
| #9        | F/35    | AML patient admitted with<br>neutropenic fever sepsis | Ampicillin and<br>kanamycin | Bacteroides sp<br>group D streptococci | Cefotaxime +<br>Gentamicin | Oral vancomycin | Died |
| Case # | Sex/Age | Diagnosis Details | Isolation Result | Isolated Organisms | Therapeutic Regimen | Outcome |
|--------|---------|-------------------|------------------|--------------------|-------------------|---------|
| #9     | F/69    | ALL patient admitted with neutropenic fever/sepsis | Positive | Bacteroides sp, Escherichia coli | Metronidazole, Ampicillin, Cloxacillin, Cotrimazole, Gentamicin | Died |
| #10    | M/62    | Splenic abscess with bacteremia | NR | Pseudomonas paucimobilis (spleen only) | Pipercillin, Netilmicin, Metronidazole | Survived |
| #11    | M/39    | Oropharyngeal cancer patient admitted with mandible radionecrosis | Positive | Escherichia coli, Enterococcus fecalis, Bacteroides vulgatos | None, Metronidazole (iv), Vancomycin(iv), Pefloxacin | Survived |
| #1     | F/85    | Nosocomial C. diff. colitis complicated by bacteremia | Positive | Enterococcus fecalis | Ticacillin/Clavulanic acid, Vancomycin(iv), Gentamicin | Survived |
| #12    | M/17    | Duchenne muscular dystrophy patient admitted with partial small bowel obstruction | NR | Candida Parapsilosis | NR, NR | Survived |
| #12    | F/33    | Cervical cancer patient admitted with pelvic abscess and recto-vaginal fistula after radiation | NR | Clostridium cadaveris, Bacteroides melaninogenicus | NR, NR | Died |
| #12    | M/77    | Perforated sigmoid diverticulum | NR | Eubacterium lentum | NR, NR | Died |
| #13    | M/3     | Tonsilitis followed by pericarditis and diarrhea | NR | None | Amoxicillin/Clavulonic acid, Cefixime | Survived |
| #14    | M/18    | Abdominal pain and diarrhea after course of antibiotics for exudative sore throat | Positive | None | Erythromycin, Oral Vancomycin | Survived |
| #14    | M/78    | Admitted after trauma, treatment for aspiration pneumonia complicated by C. difficile bacteremia | Negative | None | Cefuroxime, Amikacin, Vancomycin (oral and iv) | Survived |

**Notes:** URI, upper respiratory infection; NR, not reported; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; IV, intravenous.
reported cases of *C. difficile* bacteremia reported in the literature that are summarized in Table 1. The prevailing theory regarding the pathophysiology of *C. difficile* bacteremia is that the colonic wall inflammation associated with pseudomembranous colitis permits transient bacteremia to develop.

The overall mortality rate is significant, with 6 of 15 reported patients dying. In terms of the demographics, 11 of the 15 patients were male and the age range was from neonate to age 69. A high proportion (4 of the 15 patients) had an underlying malignancy. Unfortunately, *C. difficile* stool toxin was sent in only 7 of the patients. The stool toxin was positive in 5 out of the 7 patients. *C. difficile* Associated Diarrhea (CDAD) was reported in 6 out of the 7 patients. Two out of the 5 patients with positive stool toxin died. The majority of patients (10 of 15 patients) had polymicrobial bacteremia. Four of the reported cases occurred postoperatively.

Recent antibiotic use was found to be a significant risk factor. Antibiotic use leads to an alteration of the intestinal microflora, leading to overgrowth of endogenous *C. difficile* or allowing colonization by nosocomial *C. difficile*. Only 12 of the case reports comment on antibiotic exposure (9 of 12 patients had antibiotic exposure). Cephalosporins were the most common class of antibiotics that these patients were exposed to.

Information on therapy is available on 11 of the patients. The activity of various drugs against *C. difficile* according to the Manual of Clinical Microbiology is summarized in Table 2. Among the cases reviewed, 4 were treated with metronidazole (2 of which died). The specification of oral versus intravenous therapy was incomplete. It is important to note that the two patients who died were both neutropenic leukemic patients. There were 7 patients that were treated (at least in part) with vancomycin and they all survived except one. Two of these patients were treated exclusively with oral vancomycin and they both survived. One of the patients was treated only with intravenous vancomycin and survived. There was also one patient treated with both oral and intravenous vancomycin who survived. The remaining three patients were treated with a regimen that included other antibiotics. In our case, the patient was successfully treated with piperocillin-tazobactam.

*C. difficile* is a ubiquitous organism that can be found in the environment and exposure to the organism is common. It has been estimated that 15%–25% of adults become colonized after admission to the hospital. There is also growing literature to support a strong link between inflammatory bowel disease and *C. difficile* infection. Previous studies have demonstrated that 5%–20% of patients admitted with an IBD flare will have *C. difficile* infection. The growing literature support for the link between IBD flares and *C. difficile* infection along with the significant mortality associated with *C. difficile* bacteremia highlight the importance of this topic.

| Table 2. Activity of various drugs against *C. difficile*. |
|----------------|----------------|----------------|
| **Antimicrobial agent** | **CLSI MIC breakpoint (μg/ml)** | **C. difficile % susceptibility** |
| | **Susceptible** | **Intermediate** |
| Ampicillin | 0.5 | 1 | 26% |
| Amoxicillin-clavulanate | 4/2 | 8/4 | 100% |
| Pipercillin-tazobactam | 32/4 | 64/4 | 100% |
| Ticarcillin | 32 | 64 | 100% |
| Clindamycin | 2 | 4 | 56% |
| Vancomycin | 8 | 16 | 100% |
| Imipenem | 4 | 8 | 94% |
| Linezolid | 2 | 4 | 91% |
| Metronidazole | 8 | 16 | 100% |
| Trimethoprim-sulfamethoxazole | 32 | 64 | 26% |
| Trovifloxacin | 2 | 4 | 86% |

Clinical and Laboratory Standards Institute (CLSI) approved method M11-A6(50a); data from Wadsworth Anaerobic Bacteriology. Johnson EA, Summanon P, Finegold SM. *Manual of Clinical Microbiology*, 9th ed. 2007; 904–905.
In conclusion, we find that *C. difficile* bacteremia is associated with a significant mortality rate. *C. difficile* Associated Diarrhea (CDAD) was reported in 6 out of the 15 patients. Not surprisingly, the majority of patients had recent antibiotic exposure. We found a high proportion of patients were male. We also found that the majority of patients had a polymicrobial bacteremia. Therefore, it is unclear if *C. difficile* is the primary pathogen. In terms of treatment, it would seem prudent to consider aggressive antibiotic therapy given the high mortality rate.

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References

1. Feldman R, Kallich M, Weinstein M. Bacteremia Due to *Clostridium difficile*: Case Report and Review of Extraintestinal *C. difficile* infections. *Clinical Infectious Disease*. 1995;(20):1560–2.
2. Jacobs A, Barnard K, Fishel R, Gradon J. Extracolonic Manifestations of *Clostridium difficile* Infections. *Medicine*. 2001;(80):88–101
3. Hall IC, O’Toole E. Intestinal Flora in Newborn Infants with a description of a new pathogenic anaerobe, *Bacillus difficilus*. *Am J Dis Child*. 1935;(49):390–402.
4. Johnson S, Gerding DN, Janoff EN. Systemic and Mucosal Antibody Responses to Toxin A in patients infected with *C. difficile*. *J Infect Dis*. 1992;(166):1287–94.
5. Smith LD, King EO. Occurrence of Clostridium difficile infections of man. *J Bacteriology*. 1962;(84): 65–7.
6. Saginur R, Fogel R, Begin L, et al. Spleenic Abscess due to Clostridium difficile. *J infect Dis*. 1985;(147):1105.
7. Genta VM, Gilligan PH, McCarthy LR. *Clostridium difficile* peritonitis in a neonate. *Arch Pathol Lab Med*. 1984;(108):82–3.
8. Spencer RC, Courtney SP, Nichol CD. Polymicrobial Septicemia due to *Clostridium difficile* and *Bacteroides fragilis*. *BMJ*. 1984;(289):531–2.
9. Rampling A, Warren RE, Bevan PC, Hoggarth, CE, Swirsky D, Hayhoe FG. *Clostridium difficile* in haematological Malignancy. *J Clin Pathol*. 1985;(38):445–51.
10. Studemeister AE, Beilke MA, Kirmani N. Spleenic Abscess due to *Clostridium difficile* and *Pseudomonas paucimobilis*. *Am J Gastroenterol*. 1987;(82):389–90.
11. Gerard M, Defresne N, Van der Auwera P, Meunier F. Polymicrobial Septicemia with *Clostridium difficile* in acute diverticulitis. *Eur J Clin Microbiol Infect Dis*. 1989; 300–02.
12. Wolf LE, Sherwood GL, Granowitz EV. Extraintestinal *Clostridium difficile*: 10 Years Experience at a tertiary-care Hospital. *Mayo Clin Proc*. 1998;(73):943–47.
13. Cid A, Junca AR, Aguilera A, Regueiro BJ. *Clostridium difficile* bacteremia in an immunocompetent child [letter]. *J Clin Microbiol*. 1998;(36):1167–68. [PMID:9542965].
14. Byl B, Jacobs F, Struelsen MJ, Thys JP. Extraintestinal *Clostridium difficile* infections. *Clin Infect Dis*. 1996;(22):712.
15. Johnson EA, Summanon P, Finegold SM. *Manual of Clinical Microbiology*. 2007;9th ed:904–5.
16. Michelassi F, Taschieri A, Tonelli F, et al. An international, multicenter, prospective, observational study of the side-to-side isoperistaltic strictureplasty in Crohn’s disease. *Dis Col Rectum*. 2007;(50):277–84.