

## ***Clostridium difficile* Colitis Associated with Infant Botulism: Near-Fatal Case Analogous to Hirschsprung's Enterocolitis**

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We present the first five reported cases of *Clostridium difficile*-associated diarrhea (CDAD) in children with infant botulism caused by *Clostridium botulinum*. We compare two fulminant cases of colitis in children with colonic stasis, the first caused by infant botulism and the second caused by Hirschsprung's disease. In both children, colitis was accompanied by hypovolemia, hypotension, profuse ascites, pulmonary effusion, restrictive pulmonary disease, and femoral-caval thrombosis. Laboratory findings included pronounced leukocytosis, hypoalbuminemia, hyponatremia, coagulopathy, and, when examined in the child with infant botulism, detection of *C. difficile* toxin in ascites. CDAD recurred in both children, even though *difficile* cytotoxin was undetectable in stool after prolonged initial therapy. Four children who had both infant botulism and milder CDAD also are described. Colonic stasis, whether acquired, as in infant botulism, or congenital, as in Hirschsprung's disease, may contribute to the susceptibility to and the severity of CDAD.

The clostridia are diverse bacteria affiliated by their ability to form spores and to survive anaerobically. They cause disease through extracellular peptide toxins, such as the neurotoxins of *Clostridium botulinum* and toxins A and B produced by *Clostridium difficile*. Of these two species, *C. difficile* is more familiar to clinicians as an agent of antibiotic-associated diarrhea. This manifestation is but one point on a spectrum of gastrointestinal disease. Up to a majority of formula-fed infants are asymptotically colonized with *C. difficile* [1]. Whether colonization causes a silent protein-losing enteropathy is disputed [2, 3]. *C. difficile*-associated diarrhea (CDAD) ranges from mild diarrhea to severe pseudomembranous colitis. Toxigenic *C. difficile* has been detected in infants with lethal Hirschsprung's enterocolitis [4–6], the primary cause of death in Hirschsprung's disease.

Presented here are the first five reported cases of CDAD in those paralyzed with infant botulism, a rare illness caused by intestinal colonization with *C. botulinum*. We focus on parallel cases of fulminant *C. difficile* colitis in two children with colonic stasis, the first caused by infant botulism and the second by Hirschsprung's disease. We also describe four children who had both infant botulism and milder CDAD and reexamine an infant who was ill with colitis consistent with CDAD before testing for *C. difficile* was available.

### **Case Reports**

#### **Fulminant CDAD (Toxic Megacolon) Associated with Colonic Stasis**

*Case 1.* The initial phase of illness was typical of moderately severe infant botulism. The patient was a thriving 5-month-old white girl whose diet was breast milk, rice cereal, and fruit. She had soft, daily bowel movements. One month before onset, her family had relocated temporarily from New England to a residence near heavy construction with soil disruption in southern California, where her father had a work assignment. She developed less frequent bowel movements, a progressive inability to nurse, and weakness of cry, neck, and facial expression over 2 days (figure 1). She was admitted to the regional children's hospital for evaluation of suspected sepsis vs. abdominal obstruction.

A diagnosis of infant botulism subsequently was considered, and she was infused on hospital day 2 with human botulism immune globulin [7]. The state public health laboratory detected botulinum toxin type A and type A *C. botulinum* in her feces from hospital day 2. She required mechanical ventilation for respiratory paralysis during hospital days 3–13. She received ceftriaxone on hospital days 0–3 to treat suspected sepsis and then cefotaxime, ceftazidime sodium, and ceftazidime on hospital days 8–18 because of fever and tracheal aspirates that yielded *Pseudomonas aeruginosa*, *Branhamella catarrhalis*, and *Staphylococcus aureus*. By hospital day 21, she had regained much of her strength and tone, although feeding weakness and infrequent bowel movements persisted.

Her illness was then protracted by near-fatal pseudomembranous colitis. On hospital day 22, she began with fever, emesis, and watery stools from which leukocytes, heme, and rotavirus antigen were not detected. Diarrhea subsided within

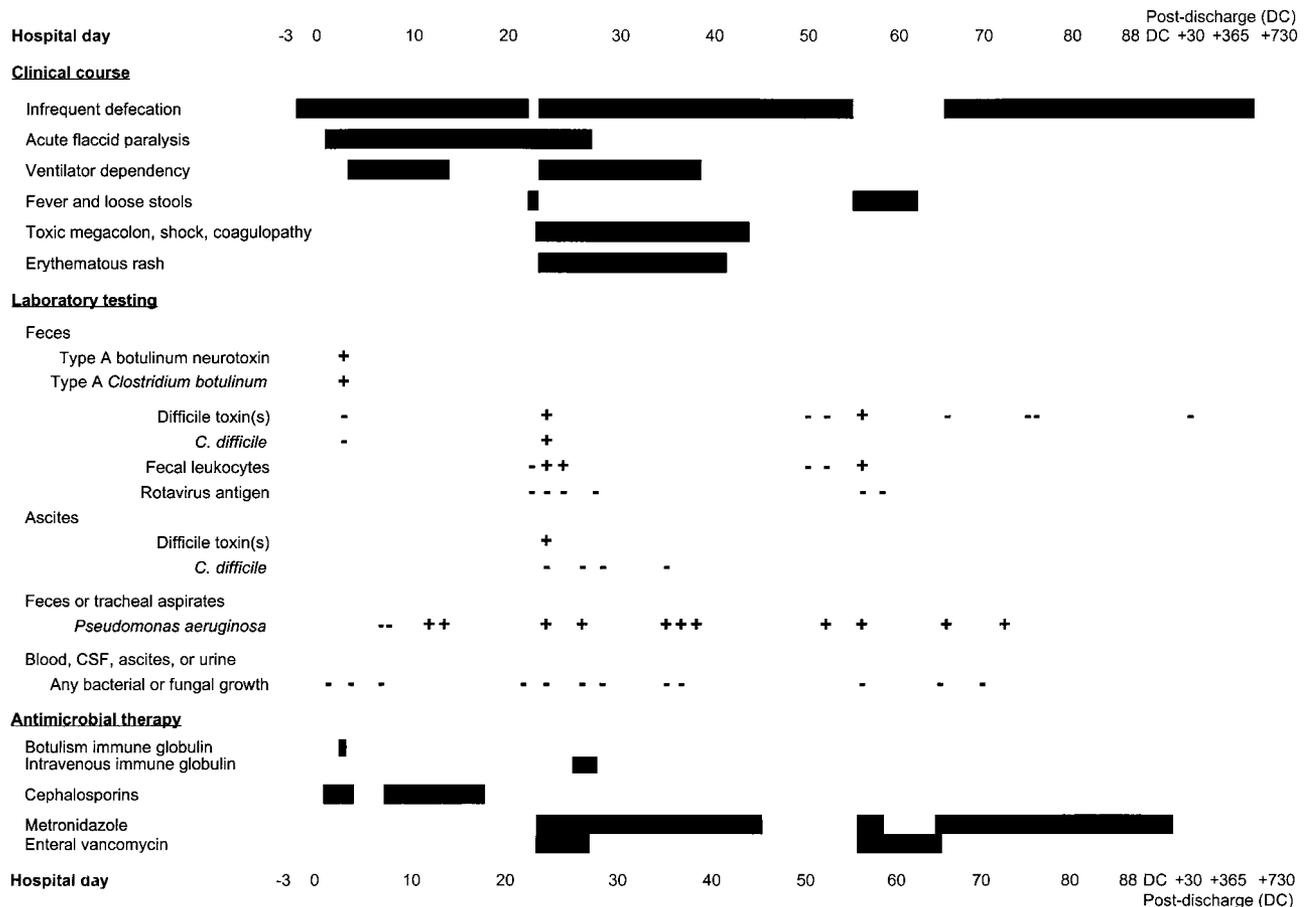
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**Figure 1.** Timing of illness for case 1: fulminant *Clostridium difficile*-associated diarrhea associated with infant botulism. DC = discharge from hospital; + = detected in laboratory testing; - = not detected in laboratory testing.

36 hours, but her serum sodium level decreased to 124 mmol/L, while her potassium level was 5.3 mmol/L. Over hospital day 23, she became lethargic with abdominal distention, emesis, and heme found in her stools. She returned to the intensive care unit on hospital day 24 with extreme abdominal distention, anasarca, poor perfusion, hypotension, hemorrhage from the sites of arterial cannulation and nasogastric tube placement, respiratory distress, and tongue thrusting as suspected seizure activity.

Blood analyses revealed the following: WBC count, 37,000/mm<sup>3</sup>, with 63% neutrophils, including 37% band forms; serum albumin, 1.8 g/dL; and serum total protein, 2.8 g/dL. During laparotomy on hospital day 24, >1 L (>15% of body weight at admission) of slightly cloudy ascites was evacuated. Although her small intestine and proximal colon appeared normal, her colon was dilated and hyperemic discretely from the midtransverse colon to rectum. There was no visible necrosis or perforation, and no bowel was resected. The colon was milked gently to evacuate stool and then lavaged with warm saline and kanamycin. A rectal tube was placed for decompression and infusion of vancomycin.

The evacuated stool contained tan and green pseudomembranes consisting of mucopurulent exudate and fibrin. Culture of stool and pseudomembranes yielded the following organisms: *P. aeruginosa* at 4+ growth; *Streptococcus faecalis*, 3+; *C. difficile*, 1+. Rotavirus antigen was not detected. Cytotoxicity of stool diluted to 1:12 was neutralized by *C. difficile* antitoxin (Bartels, Issaquah, WA) after a standard 1:3 dilution remained cytotoxic. Neutralizable *C. difficile* toxicity was detectable to 500 LD<sub>50</sub> by means of mouse bioassay. Cultures of blood, urine, CSF, and peritoneal fluid showed no bacterial or fungal growth. When peritoneal fluid was tested, *C. difficile* toxin was detected by cytotoxicity assay, but *C. difficile* did not grow on culture. Reevaluation of archived feces obtained on hospital day 2 by culture and toxin assay found no evidence of *C. difficile* or its toxins, consistent with *C. difficile* colonization occurring during hospitalization.

Treatment for *C. difficile* included vancomycin given by nasointestinal and rectal tube on hospital days 24–27 and intravenous metronidazole on hospital days 24–45. She also received ampicillin, gentamicin, imipenem, and fluconazole for *P. aeruginosa*, *Candida parapsilosis*, and other organisms iso-

lated from cultures of stool and respiratory secretions. The correction of shock required infusions of multiple vasopressors and albumin. Immunoglobulin was given intravenously at 1,200 mg/kg, both as colloid and in the attempt to neutralize *C. difficile* toxins. The patient again required mechanical ventilation during hospital days 24–39 for bilateral pleural effusions and atelectasis.

Coagulopathy was confirmed as a cause of hemorrhage; her hemoglobin level fell to 7.3 g/dL, her platelet count to 25,000/ $\mu$ L, and her fibrinogen level to 113 mg/dL, and prothrombin time was elevated to 18.9 seconds and activated partial thromboplastin time to 98 seconds. Over 10 days, she required 14 units of platelets, 10 units of cryoprecipitate, 200 mL/kg fresh frozen plasma, and 85 mL/kg packed RBCs. Computed tomographs taken on hospital day 33 and 75 displayed a thrombus extending from the left femoral vein into the vena cava up to the renal veins. The thrombus originated from the site of insertion, on hospital day 24, of a triple-lumen central catheter. An erythematous, blanching, patchy macular rash appeared on dependent regions on hospital day 24, became confluent from the nipple line to mid-thigh by hospital day 28, receded to skin folds on the trunk, legs, and left arm, and resolved by hospital day 40.

Culture of stool from hospital day 50 and 51 yielded *P. aeruginosa* (4+ growth), but *C. difficile* and its toxins were not detected. On hospital day 53, breast milk feedings were supplemented with formula. The patient had no stools over the next 2 days, after which lactulose was given. On hospital day 55, she was febrile, with loose stools initially ascribed to the stool softener. Treatment with vancomycin and metronidazole was begun on hospital day 56, and her diarrhea subsided. Leukocytes and *C. difficile* toxin were detected by cytotoxicity assay once more in her stool. She was treated with intravenous metronidazole for 3 days and enteral vancomycin for 10 days, and then with enteral metronidazole for an additional 36 days. A relative neutropenia during treatment corrected after discontinuation of metronidazole. Abundant *P. aeruginosa*, but no *C. difficile* toxin, was detected in multiple stool samples obtained after cessation of diarrhea.

On hospital day 69, the family was flown overnight to a regional children's hospital in New England. She went home on hospital day 88 with total hospital charges exceeding \$350,000. She required assistance for constipation for 1 year after discharge. Now at age 3 years, she is thriving, is no longer constipated, and has no antibodies to HIV or hepatitis C virus.

**Case 2.** As a neonate, a Vietnamese boy with trisomy 21 was diagnosed with Hirschsprung's disease. His distal colon was resected in the first week of life. He had multiple emergency room visits during infancy because of bloody or tarry stools. An endorectal pull-through (Soave procedure) was performed at age 13 months. Postoperative radiography revealed narrowing at the anorectal junction, with prolonged colonic retention of contrast.

At age 15 months, he was admitted after 2 days of poor feeding, abdominal distention, and not defecating. He had completed a course of treatment with erythromycin and sulfisoxazole for pneumonia 3 weeks previously. His vital signs were normal; his abdomen was tender, with mucoid stool palpated in the rectal vault. His WBC count was 26,000/ $\text{mm}^3$ , with 85% neutrophils, including 54% band forms. Culture of stool yielded normal flora, and blood and urine cultures showed no bacterial growth. An abdominal radiograph displayed distended loops of bowel and multiple air-fluid levels. A rectal tube was placed for decompression, enteral feedings were withheld, and treatment with intravenous ampicillin, gentamicin, and clindamycin was initiated.

On hospital day 2, half-strength formula feedings were begun, and within 5 hours, the child's abdomen became massively distended until "taut and shiny." Frequent hemochezia soon followed. His WBC count was 75,300/ $\text{mm}^3$ , with 87% neutrophils, including 51% band forms, and the following measurements were noted: serum sodium, 123 mmol/L; potassium, 4.6 mmol/L; albumin, 1.2 mg/dL. A computed tomograph of the abdomen revealed gross thickening of the distal colon, intestinal intramural gas (pneumatosis), abundant ascites, soft tissue edema, and symmetric pleural effusions with pulmonary atelectasis. On hospital day 3, he was taken to the operating room for paracentesis of 550 mL of ascites and insertion of bilateral thoracostomy tubes with removal of 150 mL of effusion. The ascites and effusion contained up to 350 leukocytes/ $\text{mm}^3$  and up to 1,800 erythrocytes/ $\text{mm}^3$ . Multiple cultures of stool for aerobic bacteria yielded normal flora. The detection of *C. difficile* toxin by cytotoxicity assay in stool obtained on hospital day 3 was reported on hospital day 11. There was no bacterial growth from cultures of peritoneal fluid, pleural fluid, or blood.

Treatment included enteral vancomycin for 5 days, intravenous and oral metronidazole for 5 weeks, and albumin infusions and cessation of enteral feeding for 4 weeks. His pulmonary effusions caused compression atelectasis, requiring mechanical ventilation during hospital days 3–24. He had coagulopathy, with the following findings: hemoglobin, 8.6 g/dL; platelet count, 15,000/ $\mu$ L; fibrinogen, 49.7 mg/dL; prothrombin time, 15.9 seconds; and activated partial thromboplastin time, >200 seconds. He was treated with 9 units of platelets, 16 units of cryoprecipitate, 115 mL/kg fresh frozen plasma, and 65 mL/kg packed RBCs. A computed tomograph on hospital day 14 detected pancolitis and a thrombus, not seen on hospital day 3, at the site of femoral vein cannulation with a triple-lumen catheter. Serial ultrasonography confirmed obliteration of the vena cava inferior to the renal veins. He received low-dose heparin for 6 months for his thrombus. His recovery from colitis was delayed by funguria and pneumonia. He was discharged home after 7 weeks with hospital charges exceeding \$290,000. *C. difficile* toxin was not found in stools from hospital day 8 and 27.

Nine days after discharge, he was hospitalized for 5 days for bloody stools attributed to excoriated diaper dermatitis. Culture of stool yielded normal flora, and detection of *C. difficile* toxin by cytotoxicity assay was reported only after hospital discharge. Three weeks later, fecaluria was noted, with contrast radiography demonstrating a rectourethral fistula. A diverting ileostomy was created and the fistula repaired. *C. difficile* toxin was detected in his stool until completion of another course of oral metronidazole. Takedown of his ileostomy 16 months later was postponed because of a tight stricture at the anorectal anastomosis, which required serial outpatient dilatations and eventually surgical incision and dilatation.

#### Less Severe CDAD Associated with Infant Botulism

**Case 3.** After having outpatient consultations with seven physicians, a 5-month-old boy was admitted because of decreased frequency of bowel movements over 6 weeks and poor feeding for a few days. An admission diagnosis of possible Hirschsprung's disease was revised to infant botulism after he became progressively weaker and flaccid. Type A botulinum toxin and *C. botulinum* were detected in his stool at the state laboratory. At hospital discharge 2 months later, he required docusate and mineral oil for infrequent bowel movements.

At age 8 months, he was hospitalized after 3 days of fever to 39.2°C and 1 day of emesis and watery, foul-smelling stools. Rectal prolapse was noted; the rectal mucosa was erythematous and covered with yellow-white plaques displaying leukocytes on microscopy. *C. difficile* toxin was detected in his stool by cytotoxicity assay. He went home the next day and was treated with a 10-day course of oral metronidazole, with resolution of symptoms.

**Case 4.** This white girl was admitted at age 3 months because of type A infant botulism and was hospitalized for 194 days because of severe paralysis. By hospital day 130, she had received intermittent antibiotic therapy for >70 days for recurrent urinary tract infections associated with urinary retention requiring catheterization. She received docusate, psyllium, and saline enemas for chronic constipation. By hospital day 135, she was again febrile, with a WBC count of 20,000/mm<sup>3</sup>, with 87% neutrophils, including 14% band forms. Her fever persisted despite treatment with intravenous cefotaxime and ampicillin and intravesical amphotericin B for the growth of group D streptococci and yeast in her urine. She did not have pyuria, and cultures of blood and CSF yielded neither bacteria nor fungi. She began to vomit and to pass mucoid diarrhea. By hospital day 142, her WBC count had increased to 28,800/mm<sup>3</sup>, with 80% neutrophils, including 24% band forms. Her stool contained many leukocytes, and cultures yielded normal flora. The detection of *C. difficile* toxin in her stool was reported 8 days after collection. By then, her antibiotic therapy had been discontinued, and her emeses and loose stools had abated.

**Case 5.** From the age of 6 weeks through childhood, this girl had a bowel movement every 1–2 weeks; this condition was treated with psyllium and dietary fiber. She was hospitalized at age 3 months for type A infant botulism. At age 9 years, she completed a 3-week course of cefixime for treatment of sinusitis. In the last week of treatment, she had left-sided abdominal cramping and loose, mucoid stools from which *C. difficile* toxin was detected. Her diarrhea resolved without hospitalization after she received vancomycin orally for 10 days. She returned to her gastroenterologist 5 months later after not defecating for 1 week; on examination, she was found to have a desiccated plug of stool in her rectum.

**Case 6.** A 3-month-old boy was hospitalized with type A infant botulism for 12 days. He had completed a 10-day course of amoxicillin for treatment of otitis media 2 weeks before admission. He received intravenous cefotaxime for the first days of hospitalization until a diagnosis of sepsis was excluded. Seven days after hospital discharge, he was readmitted because of fever and bloody diarrhea, which contained leukocytes and *C. difficile* toxin. Cultures of stool yielded *S. aureus*. His colitis subsided after treatment with oral vancomycin, and he returned home after 3 additional days. Concurrent severe diaper dermatitis resolved after topical application of nystatin.

#### "Necrotizing Enterocolitis" During Infant Botulism

**Case 7.** While acutely ill with type B infant botulism in 1976, a 6-week-old African American girl in Texas had bloody diarrhea with leukocytosis, neutrophilia, and pneumatosis intestinalis. Although not specified in her case reports [8, 9], it is probable that she received parenteral antibiotics empirically before onset of her diarrhea; blood, urine, and CSF samples were taken for culture at admission, and she required endotracheal intubation 3 days later. This episode of diarrhea was diagnosed clinically as necrotizing enterocolitis. At that time, the link between *C. difficile* and colitis was not established, and testing for *C. difficile* toxins was not yet available.

#### Discussion

In cases 1 and 2, we have described two episodes of toxic megacolon with many shared features. In both children, fever and eventually bloody diarrhea were accompanied by massive abdominal distention, an initially distal colitis, hypovolemia, hypotension, abundant ascites, bilateral pulmonary effusion, and restrictive pulmonary disease. Both children developed femoral-caval thromboses at the site of femoral vein cannulation with large-bore central catheters. Common laboratory findings included pronounced leukocytosis with increased band forms, hypoalbuminemia, hyponatremia, coagulopathy, and the detection of *C. difficile* toxin in stool. After prolonged treatment for *C. difficile* was discontinued and feces were tested without finding detectable *difficile* cytotoxin, diarrhea containing cytotoxin recurred in both children.

Given that infants can be asymptotically colonized with toxigenic *C. difficile* [1], did *C. difficile* cause these illnesses? At least five lines of evidence suggest a causal role for *C. difficile*.

First, the pathophysiology of illness was consistent for this pathogen. *C. difficile* produces two large (>275 kDa) polypeptide toxins called toxin A, or enterotoxin, and toxin B, or cytotoxin. The toxins are glucosyltransferases whose intracellular targets belong to the Rho subfamily of GTPases necessary for actin polymerization [10, 11]. The toxins are highly homologous in structure and function to those produced by *Clostridium sordellii* [12]. Both *C. difficile* toxins increase permeability by cell rounding of intestinal epithelia, while toxin A induces marked intestinal inflammation [13]. The fluid and protein loss from cell rounding could explain such findings as hypoalbuminemia, hypovolemia, ascites, and pleural effusion, while pseudomembrane formation, fever, leukocytosis, and increased band forms are consistent with vigorous intestinal inflammation.

Second, *C. difficile* toxins have been detected in feces from similar cases of severe colitis at all ages [4–6, 14–16]. The homologous *C. sordellii* toxins have been implicated in a lethal postpartum septic shock syndrome characterized by persistent hypotension, generalized edema with interstitial fluid, leukemoid reaction, and hypoalbuminemia [17, 18].

Third, the detection of *C. difficile* toxin in feces paralleled the clinical course, most notably for case 1 (figure 1). Toxin and organism were absent in the patient's stool from hospital day 2. Toxin was present in stool and peritoneal fluid at presentation of severe colitis. In both cases 1 and 2, toxin was undetectable after initial treatment and resolution of diarrhea, detectable with relapse, and undetectable after treatment of relapse. The detection of *C. difficile* toxin, but not *C. difficile*, in the ascites from case 1 during her recovery from infant botulism is distinctive and suggests that she had serial colonization and toxemia, without bacteremia, by two lethal *Clostridium* species. Previously, *C. difficile* toxin was identified by cytotoxicity assay in ascites from an infant dying of Hirschsprung's enterocolitis [19].

Fourth, clinical improvement was correlated with receiving treatment for CDAD, such as metronidazole or enteral vancomycin.

Finally, despite the severity of illness, neither child had microbial growth from cultures of samples from normally sterile sites.

Why were patients 1 and 2 so ill? Factors potentially related to the severity of their CDAD include receipt of antibiotics, colonic stasis, delays in treatment, bacterial strain, and coinfection with other microbes. Both children had received antibiotics within 3 weeks of onset of symptoms, increasing their risk for *C. difficile* colonization and disease [20]. The extensive growth of *P. aeruginosa* in case 1, and of yeast in cases 1 and

2, is consistent with a microbiota altered by the prolonged use of broad-spectrum antibiotics.

More distinctive is that each child had decreased colonic motility from either infant botulism or Hirschsprung's disease. In infant botulism, *C. botulinum* colonizes the large intestine [21], from where botulinum neurotoxin passes into the circulation. Given their proximity to the site of colonization, the colonic nerves affecting peristalsis are likely to be the nerves most heavily intoxicated. The damaged colon in infant botulism temporarily resembles the aganglionic colon of Hirschsprung's disease. Decreased stool frequency is usually the first symptom of infant botulism to appear and the last to resolve. The abdominal radiograph in infant botulism often displays dilated colonic loops [22]. With this radiographic finding and history of constipation, infant botulism may be misdiagnosed as Hirschsprung's disease, as occurred for case 3. We hypothesize that colonic stasis was a primary factor in the severity of disease.

Support for this hypothesis comes from other reports. Two children with severe pseudomembranous colitis, one of whom received no antibiotics, were given antimotility preparations to treat diarrhea 1 week before onset of severe symptoms [14, 23]. In London, 7 of 13 patients with Hirschsprung's enterocolitis had *C. difficile* toxin B detected in stool, compared with 2 of 18 with Hirschsprung's disease and no colitis [4]. Toxin B was detected in both patients who died and in all patients with abdominal distention and shock. Hirschsprung's enterocolitis associated with *C. difficile* has occurred before or after resection of aganglionic bowel [5], even without prior antibiotic therapy [6].

Colonic stasis also may increase one's susceptibility to, as well as the severity of, CDAD. Cases 3–6 developed CDAD while constipated during or after paralysis from infant botulism. A majority of adult CDAD patients in one hospital had antecedent intestinal stasis due to disease or therapy [24]. In a cohort study of 399 Seattle inpatients, receipt of stool softeners, enemas, or gastrointestinal stimulants, all therapies for constipation, were the only factors other than the receipt of  $\beta$ -lactam antibiotics associated with CDAD [20]. Colonic stasis may be a risk factor for CDAD by providing more time for colonization, proliferation, or intoxication by a *Clostridium* species. For example, a decreased frequency of bowel movements predisposed infants to contracting infant botulism [25, 26]. For case 5, chronic constipation may have been a risk factor for infant botulism during infancy and CDAD in childhood.

Delays in initiating treatment also may have affected severity. In case 1, diagnosis and treatment were deferred because the patient's diarrhea initially appeared watery and without leukocytes. Diarrhea from *C. difficile* will not be bloody until enterocytes are sufficiently damaged. When she relapsed, the diagnosis of CDAD was confounded briefly by the recent addition of stool softener for constipation. For both cases 1 and 2, as in other reports of Hirschsprung's enterocolitis, abdomi-

nal distention and shock were preceded by decreased stool output, which can be mistaken for improvement. Case 2 was initially treated with clindamycin instead of vancomycin or metronidazole.

The role of bacterial strain in the severity of CDAD is uncertain. One explanation proposed for the high frequency of asymptomatic colonization by *C. difficile* in infants is that the infant gut is more typically colonized with less toxigenic strains [27]. Culture results are consistent with case 1 being colonized during hospitalization, perhaps with a more toxic strain.

Both cases 1 and 2 would have met criteria for septic shock, which is often caused by gram-negative bacteria. It is unclear whether endotoxin (lipopolysaccharide) had any role in these illnesses. Case 1 had persistent heavy colonization of her respiratory and gastrointestinal tracts with *P. aeruginosa* before, during, and after her bouts of colitis. However, when the cytotoxicity assay and mouse bioassay were done on feces obtained during laparotomy, there was no residual toxicity detected after neutralization with *difficile* antitoxins. For case 2, other than scant growth detected in one respiratory culture, gram-negative bacilli were not cultured during his colitis. As with endotoxin, the *C. difficile* toxins induce the release in vitro of proinflammatory cytokines, such as IL-1 and TNF- $\alpha$ , from monocytes and macrophages [28, 29].

Other notable features of the two severe cases were thrombosis at the site of catheterization, hyponatremia, and rash. In elderly Swedish patients with *C. difficile* colitis, pulmonary embolism was the most frequent complication [30]. Rectal biopsies of patients with clindamycin-associated colitis revealed capillary thrombosis [31]. Thrombosis in cases 1 and 2 may have been promoted by the depletion of intravascular factors inhibiting coagulation [32, 33] because of enteropathy or pseudomembrane formation, and by central venous catheterization [34] for infusions that contained clotting factors.

Hyponatremia in toxic megacolon has been ascribed to enteral loss of electrolytes [35], yet both patients 1 and 2 were normokalemic while hyponatremic. Restoration of plasma protein levels has corrected selected cases of hyponatremia, leading to the hypothesis that hypoalbuminemia can induce hyponatremia as hypovolemia triggers the release of antidiuretic factors [36]. For case 1, hyponatremia was discovered before detection of hypoproteinemia or shock. Routine treatment for suspected syndrome of inappropriate antidiuretic hormone secretion by fluid restriction would have been perilous, and the addition of sodium alone would have been inadequate to restore intravascular volume.

A distinctive feature for case 1 was her blanching erythematous rash while maximally ill. Though we are not aware of other cases of CDAD who have had such a rash, colonic mucosal erythema is typical. Intradermal injection of *C. difficile* toxin A or B induces erythema in rabbit skin [37]. The targets of the *C. difficile* toxins, Rho proteins, participate in smooth muscle contraction [38]; perhaps the cleavage of Rho

proteins induces vasodilation and hyperemia. Although vancomycin infusion can cause the transient erythema of red man syndrome [39], she received vancomycin for only the first 3 of 16 days of rash.

Without the benefit of controlled trial, we propose tentative measures to minimize the impact of *C. difficile* in children with colonic stasis. Maximizing gut motility and promoting intestinal bacteria antagonistic to *C. difficile* may prevent colonization and infection. Tools to achieve these goals include lactulose or other osmotic agents, promotility drugs, and breast milk [1, 40], which also contains factors that neutralize *C. difficile* toxins [41, 42]. Minimizing the duration and spectrum of antibiotic therapy may be helpful in preventing CDAD. Even so, case 3 and infants with Hirschsprung's disease have developed *C. difficile* colitis without antecedent antibiotic therapy [6]. *C. difficile* has been cultured from the clothing or hands of more than half of hospital personnel caring for culture-positive patients [43]; hand-washing and environmental disinfection are recommended to limit nosocomial infection [44].

When CDAD cannot be prevented, diagnosis will be crucial and difficult. Just as the increased stool output of colitis may be initially mistaken as a desired resolution to chronic constipation, decreased output before shock may be misinterpreted as resolution of diarrhea; clinical acumen is critical in assessing these trends. Looser stools in a child with infant botulism or Hirschsprung's disease should be examined repeatedly for neutrophils, *C. difficile* toxins, and *C. difficile*. As case 1 demonstrates, an initial stool sample not displaying leukocytes or toxin may be followed shortly by positive samples. In many of the cases presented here, the results of toxin testing arrived too late to influence clinical decisions, while routine stool cultures were inadequate to detect the anaerobe *C. difficile*. These limitations may require the clinician to rely on examination for guidance on initiating therapy.

The treatment of severe CDAD is impeded by colonic stasis. Treatment with intravenous metronidazole, with or without enteral vancomycin, is warranted when gut motility is minimal. Although other antibiotics can be discontinued in milder cases, concurrent use of broad-spectrum antibiotics may be unavoidable in a critically ill child, as respiratory tract or stool cultures cannot distinguish infection by additional pathogens from colonization. Intravenous immunoglobulin contains antibodies that neutralize *C. difficile* toxins [45] and has been used to treat recurrent CDAD [46] and was used in case 1. For cases 1 and 2, aggressive medical management precluded acute bowel resection to treat fulminant CDAD. Novel medications, including probiotics [47] and enteral antibodies [48], may soon become more accessible as potential prophylaxis or therapy.

#### Note Added in Proof

Case 8. In 1999, a 6-week-old Hispanic boy developed acute flaccid paralysis while traveling with his family by car from

California to Texas. Upon admission to the hospital, he was treated empirically with single doses of intravenous ampicillin and cefotaxime. Analysis of a fecal specimen obtained on hospital day 2 revealed type A *C. botulinum*, and botulinum neurotoxin was detected, but *C. difficile* and its toxins were not detected. On hospital day 4, he began to have fever and loose stools that did not respond to intravenous vancomycin and cefotaxime. A fecal specimen yielded normal flora on culture and contained leukocytes, *C. difficile* toxin, but not rotavirus antigen. His diarrhea resolved after treatment with oral metronidazole for 7 days.

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