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Recent developments on the role of *Clostridium difficile* in inflammatory bowel disease

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Abstract

Clostridium difficile (CD), specifically its toxins, have been implicated as a risk factor for exacerbation of the inflammatory process in up to 5% of patients with ulcerative colitis or Crohn's disease. Typical evidence of colonic changes with CD infection, including pseudomembranous exudate, are often not present; however, a severe clinical course may result, including precipitation of toxic colitis and toxic megacolon. Recently, hypervirulent CD strains have been reported raising concern for a more severe disease process in patients with underlying inflammatory bowel disease. Moreover, small bowel involvement or CD enteritis has been increasingly described, usually in those with a history of a prior colectomy or total proctocolectomy for prior severe and extensive inflammatory bowel disease. Finally, refractory or treatment-resistant pouchitis may occur with CD infection.

Key words: Crohn's disease; Ulcerative colitis; Antibiotic-associated colitis; Cytotoxin; Enterotoxin; Pseudomembranous colitis; *Clostridium difficile* colitis

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INTRODUCTION

Considerable information has emerged on the intriguing relationship between the intestinal luminal microflora and the pathogenesis of inflammatory bowel disease[1]. While not believed to play an etiologic role, one particular organism, *Clostridium difficile* (CD) has become increasingly recognized as a risk factor for exacerbation of the inflammatory process in ulcerative colitis or Crohn's colitis[2]. In recent years, there has also been a marked increase in the apparent severity of disease associated with CD per se, especially with a hypervirulent strain (e.g. B1/NAP1/027) that exhibits fluoroquinolone resistance and has been detected in spite of metronidazole treatment. There have also been reports showing increased mortality and more complex CD disease with this hypervirulent strain, initially in Quebec, an eastern province of Canada, and later from other centers in North America and Europe[3-5].

CD TOXINS AND CD DISEASE

After 1977, evidence rapidly accumulated to show that toxins produced by the microbial agent, CD, rather than the organism, were responsible for significant and sometimes severe inflammatory changes in the colon, particularly pseudomembranous colitis. This usually occurred after antibiotic use that was thought to alter the normal intestinal microflora so that CD could colonize the intestine. Larson *et al*[6] made the initial observation during attempts to isolate a virus from stool of a 12-year-old female with penicillin-associated pseudomembranous colitis. Diluted fecal ultrafiltrates were toxic to tissue-cultured cells; however, this effect was not due to a viral agent. In addition, toxin concentration decreased with improved clinical status. Others examined clindamycin-induced cecitis in a hamster model and showed that vancomycin was protective, further implicating a bacterial cause[7]. Rifkin *et al*[8] showed that stool toxin from patients with the disease could be specifically neutralized in tissue culture by antitoxin. Later, toxigenic CD was cultured from fecal material of patients with antibiotic-associated pseudomembranous colitis and CD toxin was also neutralized by antitoxin.

CD causes diarrhea, often watery, rather than bloody, developing within 48 to 72 h after infection. In some, symptoms may be delayed for 2 to 3 mo, usually after an

antimicrobial agent had been administered. In some, only a single antibiotic tablet may lead to severe disease. Over time, the clinical spectrum has become better appreciated with illness severity noted to be broad ranging from an asymptomatic carrier state (without detectable toxin) to severe and life-threatening pseudomembranous colitis with toxic megacolon[2]. In others, persistent symptoms or recurrent bouts of disease develop, in part, likely reflecting the capability of the CD organism to form spores.

CD produces at least two distinct toxins[9]. These have been labeled toxin A and toxin B. Although initially thought to have distinctive actions, both now appear to be cytotoxic and enteropathic. These disrupt the actin cytoskeleton of intestinal epithelial cells by uridine diphosphate-glucose dependent glycosylation of Rho and Ras proteins[10]. Other toxins have been described, but their significance is not clear[11,12]. The most widely used laboratory assays for CD involve toxin A and/or toxin B detection and both are usually detected if diarrhea is present. Atypical toxin variant strains that may cause symptoms have also been described from Asia[13]. So far, there is no widely available clinical detection method for hypervirulent strains. Treatment for hypervirulent CD strains, however, appears to be no different from other CD infections, including oral vancomycin[14]. Recent evidence suggests that PCR (rather than the widely used ELISA assays) may not only permit detection of toxins, but also identify virulent strains, including epidemic strains[14].

CD AND INFLAMMATORY BOWEL DISEASE

CD toxin was later detected in patients with inflammatory bowel disease, especially with symptomatic relapse[15-23]. In some, no prior antibiotic administration was recorded and symptoms responded to vancomycin. Previously, some "relapses" may have been assumed to be due to "disease activity" of the underlying inflammatory bowel disease. Some thought that drugs used in medical treatment (e.g. sulfasalazine) might alter the intestinal flora and promote CD colonization[20]. Others theorized that altered immune status, possibly related to therapeutic agents, or nutritional status might be important. Pseudomembranous exudates were not always present with underlying colitis[15,17]. Also, CD toxin was detected in ileostomy fluid with symptomatically increased ileostomy output; this resolved with vancomycin. This finding suggested that CD, under special circumstances, might be able to cause small bowel as well as colonic disease[15]. Another report described toxic megacolon with CD toxin in two patients that resolved with metronidazole[23]. In both, underlying inflammatory bowel disease was noted, including Crohn's colitis and ulcerative colitis. Thus, early recognition of CD in those with known colitis might permit antibiotic treatment and reversal of toxic megacolon.

More recent investigations have confirmed and extended these early reports[24,25]. CD was the most common infecting organism in hospitalized patients with inflammatory bowel disease, recently estimated to occur in up to 5% of patients[25]. Their numbers also appear to be increasing and account for a large proportion of all patients in hospital with CD infections[24,25]. This may be due to several factors[2]: first, increased awareness of the need to test for CD toxins, particularly soon after hospital admission as many CD infections in colitis patients are community acquired; second, increased detection, due to the sensitivity of modern toxin tests; third, many hospitalized patients (including those with Crohn's or ulcerative colitis) may have other co-morbidities or reduced resistance to infection; and finally, increased use of proton pump inhibitors, antibiotics and immune modulators may also alter the normal intestinal microbial flora.

Reports have also noted the occurrence of CD enteritis usually with colitis, but very rarely as an independent small intestinal infection in the absence of colitis[26-32]. In the latter, this usually occurs after substantive colon resections, often for underlying severe and extensive colitis[28]. This is not entirely surprising since prior autopsy studies and cultures of jejunal aspirates have suggested that the small bowel per se may be a reservoir for CD[33,34]. Most often, these have been identified in elderly patients and pseudomembranous enterocolitis was found[32]. Most patients had prior gastrointestinal surgery, especially colonic resections, and usually these were patients that had a colectomy or total proctocolectomy for severe ulcerative colitis. Often, the CD infection occurred soon after colectomy, but in some, the colon resection was done even years earlier[32]. In most, a severe, often fatal, clinical course was initially noted[32], although this may now be reduced[35].

The pathogenesis has not been precisely defined. Most had prior use of broad spectrum antibiotics. As CD usually affects the colon, the factors that predispose to small bowel disease are not known. Changes in the small intestinal flora after colectomy may lead to development of a small intestinal environment similar to the colon, susceptible to CD overgrowth following antibiotic usage. Some have shown the colonic-type bacteria grow rapidly in the distal small bowel after ileocolonic resection[36]. Others have reported that the phenotypic histological changes develop in distal ileum so that colonic epithelial characteristics are seen[37]. CD toxin has also been detected in patients that have undergone pelvic pouch reconstruction[38-40]. In these, pouchitis or refractory pouchitis may be present.

CONCLUSION

The diagnosis of CD-related disease with a positive toxin assay as a cause for new or worsening symptoms in patients with underlying inflammatory bowel disease is significant as it may lead to antibiotic treatment that entirely reverses the exacerbation of clinical symptoms. Usually, disease affects the colon, but, interestingly, in patients with underlying Crohn's colitis or ulcerative colitis, pseudomembranous changes may not occur. In addition, the ileal mucosa may be at increased risk for inflammatory disease in a specific subset of patients that have undergone a prior colectomy. As a result, CD enteritis may result, possibly because the residual ileum has developed phenotypic features of the colonic luminal environment or the colonic mucosa per se. Similarly, chronic or refractory pouchitis may result from CD toxin after colectomy due

to CD colonization of the proximal small bowel, pouch mucosa or the residual rectal cuff mucosa. In these pouch patients, CD treatment may resolve the pouchitis.

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