Role of *Clostridium difficile* and *Campylobacter jejuni* in Relapses of Inflammatory Bowel Disease

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Findings from recent studies on the role of Clostridium difficile *and* Campylobacter jejuni *in exacerbations of inflammatory bowel disease are in conflict. We examined stool specimens from 32 patients who had inflammatory bowel disease in relapse for the presence of* C difficile *and* C difficile *cytotoxin. In the last 19 cases stool specimens were also cultured for* C jejuni. C difficile *was identified in one patient who was receiving antimicrobial therapy. In no patient was* C difficile *cytotoxin detected. All cultures for* C jejuni *were negative. Routine screening of stool specimens for* C difficile *cytotoxin and* C jejuni *was not clinically useful in our patients during exacerbation of their inflammatory bowel disease.*

Several bacterial agents have been associated with relapses of inflammatory bowel disease. *Clostridium difficile* cytotoxin was commonly found in some series[1-4] but not in others.[5-9] In a single report, *Campylobacter jejuni* was implicated in exacerbations of inflammatory bowel disease,[10] but no confirmatory studies have been published.

We prospectively examined the stool specimens of patients with inflammatory bowel disease in relapse for *C difficile, C difficile* cytotoxin and *C jejuni.* We were interested in determining whether these agents would be present frequently enough to justify looking for them routinely in such patients.

Methods

Patient Population

We studied 32 patients who had inflammatory bowel disease in relapse treated at several Portland area hospitals between September 1980 and July 1981. Their mean age was 36 years and the duration of disease ranged from 2 months to 18 years. Diagnosis and classification of inflammatory bowel disease were based on clinical, radiologic, endoscopic and histologic criteria.[11] In all, 8 patients had ulcerative proctitis and 13 had ulcerative colitis with more extensive involvement; 11 patients had Crohn's disease, four had colitis, three ileitis and four ileocolitis. Symptoms were graded as mild, moderate or severe using the criteria of Trnka and LaMont.[1] The ulcerative proctitis-colitis group included five patients with mild, nine with moderate and seven with severe disease. Two patients had toxic megacolon and required surgical correction. The Crohn's disease group included two with mild, six with moderate and three with severe disease. Seventeen patients required admission to hospital.

Patients were carefully questioned regarding medication taken in the prior two months: 13 were taking sulfasalazine, 7 had taken additional antimicrobial agents and 9 were receiving prednisone.

Stool Testing

Stool specimens were collected in cardboard stool containers and transported on dry ice. Most specimens were processed within two hours and all were done within 24 hours. The *C difficile* cytotoxin assay was done on sterile stool filtrates as described by Chang and co-workers.[12] Positive controls were run simultaneously.

All stool specimens were cultured for *C difficile* using a selective medium incorporating cycloserine and cefoxitin.[13] Positive controls were run simultaneously. Colonies resembling *C difficile* were subcultured onto

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10 percent sheep blood agar and identified by an API (Analytab Products Inc, Plainview, NY) anaerobic biochemical strip.

After the report suggesting that *C jejuni* is associated with relapses of inflammatory bowel disease came to our attention,[10] stool specimens were also cultured for this organism, using a Campy-BAP medium (Baltimore Biological Laboratories, Cockeysville, Md), a selective culture medium for C *jejuni*.[14] Differentiation of *C jejuni* from other *Campylobacter* subspecies was made by detecting growth in brucella broth at 37°C and 42°C but not at 25°C.[14]

Results

The *C difficile* cytotoxin assay was negative in all 32 patients. *C difficile* itself was identified in the stool of one patient with severe ulcerative colitis; cytotoxin, however, was not present. This patient was receiving several antimicrobial agents at the time of the positive culture. He responded to conventional therapy for inflammatory bowel disease. Vancomycin was not given, and because he became asymptomatic we did not reculture specimens of stool.

C jejuni was not identified in any of the 19 patients tested.

Discussion

Inflammatory bowel disease is characterized by periods of relative well-being interspersed with flare-ups of activity. Severe relapses may lead to hospital admission and on occasion require a surgical procedure. If, as some reports suggest, treatable pathogens such as *C difficile* or *C jejuni* are frequent causes of disease exacerbation, examining all patients in relapse for these agents would be important. If they are infrequently found in patients with inflammatory bowel disease, however, routine screening may not be justifiable. It is therefore important to establish how often and under what circumstances relapses of inflammatory bowel disease are in fact associated with these agents.

Whereas our findings are in concert with several studies, others have reported *C difficile* cytotoxin in up to 60 percent of patients with a severe relapse of inflammatory bowel disease[1] and *C jejuni* has been found in 10 percent of inflammatory bowel disease relapses.[10] Possible explanations for these discrepant results include differences in test methods, patient population and local epidemiology.

Technical aspects of our study were comparable to those that suggested a significant role for *C difficile* cytotoxin in inflammatory bowel disease.[1-4] Unlike prior investigations, however, we also examined stool specimens for the organism itself. Our negative culture results in all but one case are further evidence against a significant role *C difficile* in relapses of inflammatory bowel disease in our patients, even though loss of viable organisms during transport could theoretically have occurred. Transport losses likewise may conceivably have resulted in false-negative cultures for *C jejuni,* though prompt inoculation of the culture medium in most cases makes false-negative results unlikely. A theoretically more important cause of false-negative cultures is that many patients were taking antibiotics, especially sulfasalazine. Unfortunately, the sensitivity pattern of *C jejuni* to this drug is not known.

Our patient population was comparable to that in other studies in terms of severity of symptoms and frequency of prior antimicrobial exposure. Of the 32 patients, 26 had moderate or severe disease and 17 were admitted to hospital. About half were receiving sulfasalazine or other antimicrobial agents (or both). Of the 19 patients who had stool specimens cultured for *C jejuni,* 15 had moderate or severe symptoms.

Epidemiologic factors seem the most likely explanation for the variable frequency with which *C difficile* has been found during exacerbation of inflammatory bowel disease. Recent reports have suggested that disease due to *C difficile* can be nosocomially transmitted,[15,16] and older studies of pseudomembranous colitis showed geographic and temporal clustering.[17] Series with high recovery rates of *C difficile* toxin may reflect such clustering.

We conclude that in our local hospitals neither *C difficile* nor *C jejuni* are significant agents in inflammatory bowel disease and routine screening for these pathogens in all patients with inflammatory bowel disease in relapse cannot be justified. In selected situations, however, investigation may be indicated. With *C difficile,* this would appear to be most compelling when antimicrobial agents have been administered within two months of the onset of disease symptoms. Examination for *C difficile* or *C jejuni* is also indicated in patients with exacerbation of inflammatory bowel disease during known local outbreaks and in those who fail to respond to routine treatment.

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