Clostridium Difficile Infection in Patients with Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) are at higher risk of developing Clostridium difficile infection (CDI) than are those without; patients with both IBD and CDI also appear to have poorer outcomes than those with CDI alone. Stool tests for CDI should be requested in all IBD patients presenting in diarrhoeal relapse. Treatment of CDI complicating IBD should be the same as in patients without IBD, but it is not yet clear whether concurrent corticosteroids and/or immunomodulators should be withheld.

CLOSTRIDIUM DIFFICILE – BACKGROUND

Clostridium difficile (C. difficile) is a Gram-positive anaerobic spore-forming bacillus which was first described as a human pathogen in 1978. C. difficile is found in the colonic flora in up to 4% of healthy adults. C. difficile produces two main toxins (A and B), which are both potent entero- and cytotoxins. Patients can be said to have CDI only when they have diarrhea and have had a confirmatory stool investigation. The latter is now commonly a 2-step process. The first step has a high negative predictive value and should either be a glutamate dehydrogenase detection assay or a polymerase chain reaction for the presence of C. difficile organisms: if samples test positive by either of these methods, the second step is a sensitive ELISA to detect toxin.

CDI rates rose sharply in the early 2000s with several well-documented outbreaks in North America and in Europe. Despite more vigilant infection control practices and greater clinical awareness, rates of CDI in the USA continue to rise. CDI remains a hugely important healthcare issue in that hospitalized patients with CDI are nearly 3 times more likely to die during their admission than other inpatients.

The most common risk factor for CDI is concurrent or recent antibiotic use, with risk persisting for up to 3 months after antibiotic use. Other predisposing factors include increasing age, and, for inpatients, prolonged length of hospitalization prior to acquisition, co-morbidities such as renal failure, use of proton pump inhibitors, chemotherapy and enteral feeds. In the last 20 years, it has become clear that IBD is a major risk factor, and this has led to a recognition of the need for heightened awareness and testing in this group.
risk factor for CDI, and the aim of this paper is to review the incidence, presentation, diagnosis, treatment and outcome of CDI in patients with pre-existing ulcerative colitis (UC) or Crohn’s disease.

INCIDENCE OF CDI IN PATIENTS WITH IBD

CDI in Patients with Active IBD

Over a range of single center studies analyzed for a recent systematic review, the incidence of CDI in adults presenting with relapse of their IBD was about 7-9%, reported rates varying between 2.5 and 15%, with no overt difference between UC and Crohn’s disease. In contrast, in four studies which used diagnostic coding in hospitalized patients in the US, the co-incident rate of CDI and UC was about 3%, and of CDI and Crohn’s 1%, both higher than in the control populations (0.5%). In two studies of children with active IBD, CDI was more common, with an incidence of 16 and 36%, respectively. This may be because feco-oral ingestion of spores is more common in children than in adults, or because children are more likely to have colonic Crohn’s disease and to have extensive UC (see below).

CDI in patients with inactive IBD

A prospective study of outpatients with inactive IBD who were not taking any immunosuppressants showed a carriage rate of *C. difficile* of 8% compared to 1% in healthy controls; furthermore, in IBD, the strains of *C. difficile* found in stool were those not normally associated with nosocomial infection. In a six-month follow up period, none of these patients developed CDI.

Figure 1. Suggested management algorithm for CDI in IBD patients. Treatment failure is defined as persistence of diarrhea for 7 days or clinical deterioration.
This may explain the observation that most patients with IBD contract their CDI from multiple community sources rather than nosocomially.12

**Is the Incidence of CDI in IBD Increasing?**

Although single center studies show no temporal trend over the years 1980–2010 in the incidence for CDI in IBD patients,12 data from multicenter studies using either diagnostic coding13-16 or stool toxin to confirm infection20, 21 all suggest a steady increase in incidence of this infection in the last 10 years.

**RISK FACTORS FOR CDI IN PATIENTS WITH IBD**

**Age and Co-morbidity**

In adults with IBD, as in the general population, increasing age and co-morbidity increase the risk of acquisition of CDI.15 However, the average age of cohorts of patients with concurrent CDI and IBD is much lower than in the general population, suggesting that patients with IBD have different risk profiles.

**Medication**

Although antibiotic use remains its major single risk factor, only half of IBD patients who contract CDI have had prior antibiotic exposure.12 This further highlights the different risk profiles for CDI in IBD patients.

Immunomodulators are increasingly prescribed to treat IBD and one retrospective series found that the use of immunosuppression (including corticosteroids, thiopurines and methotrexate) in IBD doubled the chance of developing CDI.20 In contrast, another study found that while steroids increased the risk of CDI 3-fold, infliximab and immunomodulators had no detectable effect.22

**Location of IBD**

Perhaps unsurprisingly, patients with UC and colonic Crohn’s are at higher risk of CDI than patients with isolated small bowel Crohn’s disease.16, 20, 23 Furthermore, patients with extensive UC are at greater risk than those with distal disease.20 Rare cases of CDI enteritis24 and pouchitis25 have also been reported in patients who have had colectomies for ulcerative colitis.

**Presentation**

CDI in IBD presents in the same way as in the non-IBD population, with diarrhea, pyrexia and raised inflammatory markers, all features shared with active IBD alone. The diarrhea associated with CDI is not normally bloody but this is not a reliable diagnostic feature. In hospitalized patients being treated for a relapse of their IBD, a sudden worsening of symptoms or fever, or a rise in C-reactive protein or white cell count should raise suspicion of incident CDI.

**Diagnosis of CDI in IBD**

As in the non-IBD population, this is done by requesting microbiological stool investigations (see above) and only diarrheal stool should be tested.

Most patients with CDI complicating IBD do not develop pseudomembranes,26 making flexible sigmoidoscopy an unreliable way of diagnosing CDI in this setting, although it can of course be useful in assessing the activity of the associated IBD.

**Management of CDI in IBD (Figure 1.)**

There is no IBD-specific trial data to guide management of CDI in patients with IBD. At present, the principles of antibiotic usage are similar to those for patients without IBD,27 the options being oral or intravenous metronidazole and oral vancomycin. A new agent, fidaxomicin, has been licensed by the FDA for use in CDI but the relevant phase III trial excluded patients with IBD.28 There is no evidence on which to base decisions about treatment of patients with IBD with apparently refractory CDI or with recurrent CDI.

However, in patients still unwell after several days of treatment of their CDI with an appropriate antibiotic regimen, consideration should be given to flexible sigmoidoscopy and biopsy, in case their non-response is due to a flare of their IBD rather than persisting CDI. Cytomegalovirus (CMV) infection should also be sought and excluded by serology, plasma CMV quantification and biopsy in this situation.

What to do about concurrent immunosuppression is also uncertain at present.29 A retrospective series reported a worse outcome when CDI complicating IBD was treated with a combination of antibiotics and immunosuppressants rather than with antibiotics alone,30 but prospective data is lacking. Nevertheless, it is probably sensible to withhold immunosuppressants temporarily in patients seriously ill at presentation, and to avoid initiating them or increasing their dose until CDI treatment has been completed. Patients on anti-TNF agents should have their next dose delayed until CDI has been cleared. This advice, however, may, after (continued on page 23)
further investigation (see above), need reversing in patients with persisting symptoms, despite apparently appropriate antibiotic therapy, which are considered to be due to active underlying IBD.

Response to Treatment

In patients without IBD, overall failure rates for metronidazole and vancomycin are 26% and 6% respectively, while use of fidaxomicin is associated with fewer recurrences than occur with vancomycin 125mg QID. There is no data for the failure rates of these agents in patients with IBD. A database study reports that, as in the non-IBD population, low serum albumin and a rise in serum creatinine are predictors of a bad prognosis of CDI in IBD.

Outcome of CDI in IBD

Several studies report poor outcome of CDI in IBD, with reported colectomy rates during the acute phase of up to 20%. Furthermore, patients with CDI complicating their UC seem to have a worse prognosis for surgery during the succeeding year, with about 40% needing colectomy compared with 4-25% of patients with UC alone. Length of stay (up to 28 days longer than in controls with IBD alone) and mortality (up to 14% compared with 2.5% in controls) are also increased in patients hospitalized with both CDI and IBD according to large diagnostic coding-based studies. It is worth emphasizing that much of this data relates to hospital admissions in the early 2000s, when the association between CDI and IBD was less well recognized and may have been less well managed than it should be now.

Prevention of CDI in IBD

As in all patients with CDI, isolating infected patients to prevent spread, and washing hands with soap and water are essential. Particular care should be taken in prescribing antibiotics to patients with IBD. Empirical use of broad-spectrum antibiotics should be avoided and, when antibiotics are deemed essential, the clinical purpose should be clearly defined.

CONCLUSION

CDI in IBD patients is an increasing concern in relation to both its incidence and outcome. C. difficile should be sought whenever an IBD patient presents with diarrhea. Flexible sigmoidoscopy in IBD and CDI rarely shows pseudomembranes and should not be relied on to diagnose CDI.

In the absence of IBD-specific clinical trials to date, treatment of CDI in IBD should be as for the non-IBD population. In patients initially presenting seriously ill, withholding of concurrent immunosuppression may be advisable. More prospective studies are required to understand the implications of CDI in IBD and to optimize its management.

References