Clostridium difficile, sulphasalazine, and ulcerative colitis

D.A. Burke and A.T.R. Axon

Gastroenterology Unit, The General Infirmary, Leeds, LS1 3EX, UK.

Summary: Clostridium difficile has been implicated in the relapse of ulcerative colitis. Controversy exists over this role and its relationship to sulphasalazine exposure. Sixty two of 77 patients with a documented relapse of ulcerative colitis were investigated for the presence of Clostridium difficile, or its toxin, prior to hospitalization. There was a low incidence of detection which was related to antibiotic exposure (2/62). Sampling during the treatment period showed that the occurrence of Clostridium difficile in the stool was related to antibiotic treatment (2/66). Fifty six percent of patients were taking sulphasalazine, none of whom became culture or toxin positive. This study demonstrates that Clostridium difficile is not related to relapse of ulcerative colitis and is not secondarily acquired during relapse unless the patient is exposed to antibiotics. Sulphasalazine does not predispose to acquisition of Clostridium difficile. There is no role for routine screening or treatment of Clostridium difficile in ulcerative colitis.

Introduction

The role of Clostridium difficile in inflammatory bowel disease and its relationship to sulphasalazine exposure is controversial. Studies from different parts of the world have suggested that it may cause relapse1,2,3 whilst others have disputed this.4,5,6 Sulphasalazine has been proposed as a predisposing factor5 and a protective factor.7 Variations in sampling, timing of collection, absence of either culture or toxin results, and population differences may contribute to some of the discrepancies in these studies. Detection of the organism or its toxin during a relapse of inflammatory bowel disease cannot necessarily implicate it in the causation of the relapse without taking into account the temporal relationship of its appearance during the attack in order that secondary acquisition can be excluded. Alternatively, changes in the faecal ecology secondary to the disease process may facilitate detection of the organism in inflammatory bowel disease.

Because of the diagnostic and therapeutic implications of this organism having a role in inflammatory bowel disease this study was undertaken to investigate Clostridium difficile in patients presenting with a relapse of ulcerative colitis.

Patients and methods

Stool samples were obtained from patients with an acute attack of ulcerative colitis attending the inflammatory bowel disease clinic. The diagnosis was established by endoscopic and histological criteria. Stool was collected into sterile universal containers, immediately dispatched to the laboratory, and maintained at 4°C during analysis. Stools were collected in the outpatient department on presentation in all outpatients and most inpatients; where this was not possible samples were obtained within 12 hours using disposable containers to eliminate contamination.

Seventy seven patients with an acute relapse of ulcerative colitis were studied during the period October 1984 to March 1986 (42 males, 35 females) age range 19–75 (mean 42.6). Twenty patients had disease limited to the rectum, in 27 the disease involved the left side of the colon, and 30 patients had disease extending beyond the splenic flexure. Nine patients had severe disease, 49 moderate, and 19 mild (Truelove and Witts criteria).9 The length of history of the attack ranged from 3 days to 52 weeks (median 6 weeks). Thirty five patients were actively taking sulphasalazine, another 27 had received it at some time in the past, and 5 were receiving 5-amino salicylic acid.

Clostridium difficile was isolated under anaerobic conditions using CCFA Agar (Cefoxitin, Cycloserine, Fructose Agar). Toxin was detected by examining stool supernatant, for a cytopathic effect on HeLa cells which could be neutralized by Clostridium sordelli antitoxin. In addition stool was routinely cultured for salmonella, shigella and campylobacter species.

Results

Sixty two patients were able to supply a suitable stool sample prior to commencing treatment. Only 1 patient had a positive culture for Clostridium difficile but had

Correspondence: D.A. Burke M.B., B.S., M.R.C.P.
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no detectable stool toxin, he had been treated with co-
trimoxazole for a chest infection and his symptoms
resolved when the antibiotic was withdrawn. Another
patient was found to be culture negative, but toxin was
detected at very low titres (1:2), there had been no
history of antibiotic exposure in this case. Only 4
patients had received antibiotics 1–2 months before
the onset of their symptoms, and only 1 of these was
culture positive.

There were 9 patients in whom no initial stool
sample was obtained, but who provided a specimen
during the course of treatment. All of these were
negative for culture and toxin. Stools were assayed in
a further 57 patients during treatment. Two cases were
culture positive for Clostridium difficile but no toxin
was detected. Both had received antibiotics during the
treatment period, 1 patient in hospital the other as an
outpatient. The inpatient was given vancomycin 125 mg t.d.s. orally on the basis of the positive culture
result despite the fact that recovery from his colitis did
not show any relapse in relation to antibiotic treat-
ment or positive stool culture result. Three inpatients
who required emergency colectomy were all Clo-
stridium difficile negative at presentation. Six patients
did not have Clostridium difficile culture or toxin assay
before or during treatment but they all responded to
treatment appropriate for their colitis. In no case was
any other bacterial pathogen isolated before or during
treatment.

Discussion

Reports in 1980 of an association with relapse of
inflammatory bowel disease and the presence of
Clostridium difficile or its toxin in the stool led to the
suggestion that it might have a role in the relapse of
IBD. Further studies have both supported and
refuted this view. Explanations put forward for the
disparity in these reports have included population
differences in patient groups, non-specificity of the
toxin assays used, together with the absence of support-
ive culture results. The timing of cultures in relation
to presentation and hospital admission has not been
adequately documented and, because of this, stool
Clostridium difficile positivity as a consequence of
secondary acquisition during a period of active inflam-
mation could not be excluded. Cultures obtained from
hospitalized patients may represent nosocomial
spread.

In this study we have eliminated some of these
problems by studying a group of patients whose
diagnosis had been sigmoidoscopically and hist-
ologically substantiated, and by collecting samples
before the patient was admitted to the hospital
environment to eliminate nosocomial contamination.

Furthermore, both culture and toxin assay were
undertaken before and during treatment to detect any
secondary colonization with Clostridium difficile.

Our results show that Clostridium difficile is not
associated with relapse of ulcerative colitis and furth-
ernore it is not acquired during the period of active
inflammation even in those patients in hospital where
during the study period there were sporadic cases and
even clusters of Clostridium difficile-associated diarr-
hoea in other patient groups throughout the hospital,
indicating that the organism was probably in the
environment. Barrier nursing is not normally
employed for our colitic patients and they are man-
aged on general medical and surgical wards through-
out the hospital. Very few patients had been exposed
to antibiotics, other than sulphasalazine. Only 1
patient appeared to have symptoms in association
with a positive stool culture and in this case there was
an identifiable antibiotic aetiology.

The fact that 56% of our patients were taking
tsulphasalazine and none of them became culture
positive does not support the view that sulphasalazine
predisposes to the development of Clostridium difficile
associated disease. In vitro studies demonstrating the
inhibitory effect of sulphasalazine, sulphapyridine and
to some extent 5-amino salicylic acid on Clostridium
difficile also refute the suggestion of Greenfield et al.

The cost of culture and toxin assay is approximately
£5.00 per sample in a laboratory with established
tissue culture facilities, and the cost of treatment
for five days with vancomycin 125 mg t.d.s/day is about
£45.00. Consequently it would require considerable
expenditure in time, and money to undertake either
routine diagnosis or treatment of Clostridium difficile
in patients with ulcerative colitis. Furthermore toxin
assay is not readily available in all centres.

Patients with inflammatory bowel disease may
respond to treatment with vancomycin. This observa-
tion would appear to add support to the theory that
Clostridium difficile is involved in relapse, but it does
not follow that the improvement is necessarily related
to its activity against Clostridium difficile. A recent
study from Dickinson et al. showed that there was a
trend towards improvement in those treated with
vancomycin but that it was not related to eradication
of Clostridium difficile. It is therefore possible that its
benefit is not related to its antibiotic potential, but
some other property, just as metronidazole has been
shown to be of benefit in Crohn's disease, possibly
due to its in vitro immunosuppressive activity.

This study shows that Clostridium difficile is not
involved in relapse of idiopathic ulcerative colitis, and
that consequently there is no need to screen for
Clostridium difficile unless there is a history of
antibiotic exposure. Patients with ulcerative colitis
may develop infection with Clostridium difficile follow-
ing antibiotic exposure as any other patient group.
References

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