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(*Accepted 2 October 1981*)

Clostridium difficile in association with sporadic diarrhoea

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Abstract

A total of 154 patients admitted to an infectious diseases unit were included in a year's prospective survey of sporadic diarrhoeal disease. Stools from 19 of them yielded Clostridium difficile, generally on more than one occasion. Twelve of these patients were assessed as having a severe or moderately severe gastrointestinal illness: Cl difficile was the only pathogen isolated from 10 of them, and two had an associated salmonella infection. Seven had had a recent course of antibiotics, but five had not taken antibiotics. Faeces from seven patients with moderate or mild gastrointestinal illness yielded Cl difficile, and two of these patients also had an associated salmonella infection. Two patients in this group had no antibiotic history.

From these findings, the occurrence of C difficile in faeces could not be described as antibiotic-associated. Faecal Cl difficile cytotoxin was detected in only six patients, and generally at low levels. In such patients a more relevant pathogenic index might take account of the numbers of Cl difficile present and of their toxigenic potential.

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Introduction

Though a pathogenic association between *Clostridium difficile* and pseudomembranous colitis is accepted, the role of this organism in intestinal health and disease in infants and adults is still uncertain.[1] The development of better selective culture procedures has greatly facilitated the isolation of *Cl difficile* from stools.[2] We have therefore conducted a prospective study to determine the range of circumstances in which *Cl difficile* may be detected and possibly implicated in sporadic cases of diarrhoea in adults admitted during one year to an infectious diseases hospital.

Patients and methods

We included in the survey all patients admitted to the infectious diseases unit during November 1979 to October 1980 who presented with diarrhoea or developed diarrhoea. During the study period there was no recognised epidemic of gastroenteritis or diarrhoeal

disease. Diarrhoea was defined as three or more loose stools daily for one day or more. The stools of patients with diarrhoea were examined for intestinal pathogens, including *Salmonella*, *Shigella*, and *Campylobacter* spp and for *Cl difficile;* a sample of faeces was also referred for virological examination but not for direct electron microscopy. Patients whose stools yielded *Cl difficile* were graded retrospectively according to the severity of their illnesses on clinical grounds alone.

BACTERIOLOGICAL INVESTIGATIONS

Specimens of faeces—Samples were taken with care to avoid contamination and submitted in sterile plastic containers without transport medium. When *Cl difficile* was isolated follow-up specimens were submitted.

Microscopy—Suitable preparations of each specimen were examined by phase-contrast microscopy; a Gram smear was prepared and examined by light microscopy. Pus cells, red blood cells, and Gram-positive rods with spores were noted.

Culture—Approximately 0·1 g or 0·1 ml of faeces was plated on cefoxitin cycloserine fructose agar medium (CCFA)[2] and incubated anaerobically in 90% hydrogen and 10% carbon dioxide for 24 hours at 37°C. Another, similar sample was inoculated into Robertson's cooked meat broth and incubated in the same way. The CCFA plate was examined for typical colonies, and the number of *Cl difficile* in the faeces estimated semi-quantitatively: + = growth in well only (10^2-10^3 organisms/g faeces), + + = growth in well and on primary streaks (10^3-10^4), and + + + = growth in well, primary streaks, and secondary streaks ($\geqslant 10^5$). The cooked meat broth culture was plated on CCFA medium and this plate subsequently examined for *Cl difficile* and scored ± if positive only after enrichment. All CCFA plates were incubated for 48 hours before being discarded as negative. All presumptive isolates were confirmed by gas chromatography of the volatile fatty-acid products of metabolism. The acidified supernate from a 24-hour culture in proteose peptone, yeast extract, serum, and glucose medium[3] was examined on a column of 15% Supelco SP1220, 1% H_3PO_4 on chromosorb W acid washed in a Pye Unicam model 104 gas chromatograph. A typical fatty-acid profile with pronounced peaks of acetic, N-butyric, isobutyric, N-valeric, isovaleric, and isocaproic acids was taken as diagnostic.

Toxin assay—Toxin was assayed essentially according to Bartlett[4] by observing a cytopathic effect on monolayers of human embryonic fibroblast cells. All faecal assays were performed retrospectively on specimens that had been stored at −18°C. Before centrifugation, solid faecal specimens were mixed with a minimum of physiological saline to give a fluid suspension; liquid specimens were used without further dilution. Neutralisation tests were performed with *Cl sordellii* antitoxin (10 µl of a one in 25 dilution added to 90 µl medium over the monolayer just before adding 10 µl of faecal extract). The toxigenicity of fresh isolates of *Cl difficile* was estimated by assaying the supernate from five-day cultures in 3·5% (w/v) brain-heart infusion medium supplemented with 1% (w/v) proteose peptone (both from Oxoid).

Results

A total of 154 patients were included in the survey, 145 of whom were referred by their general practitioners and nine transferred from other hospitals. All were admitted for investigation and treatment of illnesses that either presented with or developed a diarrhoeal phase. Of these, 39 had medical or surgical conditions that might reasonably be associated with diarrhoea and not regarded as primarily infective. Of the remaining 115 patients, 27 (23%) yielded enteropathogenic bacteria, 12 (10%) had salmonella infections, and 15 (13%) yielded campylobacters. A reovirus may have caused another one diarrhoeal episode. From four of our 115 patients a *Salmonella* sp and *Cl difficile* were isolated together. Eighty-seven patients had diarrhoea that might have been infective and was unexplained; from 15 of these we isolated *Cl difficile* alone.

During the survey 35 patients were admitted who did not fulfil the criteria of the study—that is, they did not produce three or more loose stools daily for one day or more. Stools from these patients were also investigated and contained no *Cl difficile*. Since other patients resident in hospital are not entirely equivalent, the 35, like the study patients, were in the main admitted directly from the community, were regarded as matched controls.

Cl difficile was isolated from a total of 19 patients (group 1). Of these, 17 came from their homes and two were from other hospitals. The age range was 19 to 88 years, with a mean of 56; the male to female ratio was 1:4; two patients died; 15 of the patients presented during May to October: and one had travelled abroad recently. There was no case-to-case spread of *Cl difficile*. On only one occasion were two patients with the organism in the ward at the same time. A check on the ward area and clean bedpans during the survey yielded no *Cl difficile*.

Toxin that could be neutralised by *Cl sordellii* antitoxin was detected in the faeces of six patients in group 1. No cytotoxin was detected in any of the specimens that were available for testing (106 tested out

Details of 19 patients from whom Cl difficile was isolated (group 1)

Case No	Age and sex	Severity of illness	Antibiotic or steroid history	Other enteric pathogens isolated	Other illnesses diagnosed	*Cl difficile* isolated	In-vitro toxigenicity titre	Faecal cytotoxin* titre	Treatment and comment
1	42 F	+ + + +				+ +	1 000	64	Vancomycin
2	69 F	+ + + +	Co-trimoxazole†		Rheumatic heart disease	+ + +	100	1 024	Vancomycin. Died
3	55 F	+ + + +			Diabetes, chronic obstructive airways disease	+ +	100	§	Vancomycin
4	77 F	+ + + +			Ischaemic heart disease, chronic obstructive airways disease	+ + +	10 000	§	Vancomycin
5	88 F	+ + + +	Ampicillin + flucloxacillin		Ischaemic heart disease	+ +	1 000	16	Vancomycin, cholestyramine
6	40 M	+ + + +			Cerebral cortical atrophy	+	§	§	Vancomycin
7	24 F	+ + + +	Erythromycin	*Salmonella panama*‡		+ +	10	4	Vancomycin, chloramphenicol
8	65 F	+ + + +	Prednisone, co-trimoxazole,† cefuroxime†	*Salmonella derby*	Rheumatoid arthritis	+ + +	10 000	1 024	
9	87 F	+ + +	Ampicillin		Chronic obstructive airways disease	+	100 000	ND	
10	19 F	+ + +	Penicillin, cephradine, prednisone		Panhypopituitarism	+ + +	10	§	Vancomycin
11	85 F	+ + +			Ischaemic heart disease, hypothyroidism	+	10 000	§	Vancomycin
12	44 F	+ + +	Doxycycline			+	§	§	Cholestyramine (failed), vancomycin
13	50 F	+ +	Ampicillin		Colostomy, diverticulosis	+ + +	100 000	§	Vancomycin
14	84 F	+ +			Secondary myocardial infarction	+	100	§	
15	37 M	+	Oxytetracycline		Hand, foot, and mouth disease	+	100	§	
16	79 M	+	Ampicillin, flucloxacillin†	*Salmonella agona*	Femoral popliteal bypass	+ +	10	16	
17	75 M	+	Chloramphenicol, amoxycillin,† erythromycin	*Salmonella virchow*‡	Chronic obstructive airways disease, pneumothorax	+	§	§	Died from chronic obstructive airways disease
18	19 F	+	Flucloxacillin, lincomycin†		Staphylococcal skin sepsis and eczema	+ + +	§	§	
19	19 F	+				+ +	§	§	

ND = Not done.
‡Organism also isolated from blood cultures.
*Neutralised by *Cl sordellii* antitoxin.
§Not detected in undiluted extract.
†Diarrhoea developed while taking drug.

of a possible 135) from patients who did not have *Cl difficile* in the faeces (group 2). Twelve of the 19 patients in group 1 and 17 of the 135 in group 2 had had courses of antibiotics during the six weeks before their admission to hospital, whereas only one of the 15 patients with campylobacter diarrhoea and none of the eight with salmonella infections alone had received antibiotics during that time.

There was no appreciable difference between the two groups in age, sex, mortality, seasonal incidence, contact history, or travel abroad, and the groups were indistinguishable in terms of presentation, biochemical and haematological profiles, and clinical course. Group 2 included a wide variety of acute surgical cases (appendicitis, perforated viscus, obstructed hernia, ischaemic ileitis, and colitis) and medical conditions (diverticular disease, carcinomatosis, pneumonias, ulcerative colitis, and chronic renal failure). There was no obvious correlation with faecal excretion of *Cl difficile* in patients with diarrhoea other than recent antibiotic treatment, which was not an invariable association.

Clinical assessment—The table summarises relevant data for the 19 patients in group 1. The patients were divided retrospectively into four groups based on the severity of their illness; duration, frequency, and persistence of diarrhoea; occurrence of blood in the stools; fever; signs and symptoms of dehydration; increased white cell counts; and low serum albumin concentrations. The four groups were clinically severe (++++), moderately severe (+++), moderate (++), and mild (+). We considered that 12 patients had appreciable enteropathy, and it was among these that the high white cell counts and low serum albumin values were recorded. The symptoms included diarrhoea, vomiting, and abdominal pain; three patients had frank blood in the stools.

Microbiological assessment—Semi-quantitative assessments of the isolation of *Cl difficile* from the 19 patients in group 1 showed many examples of poor correlation with clinical severity. This was also true of our assessments of in-vitro toxigenicity of the *Cl difficile* isolates and it was largely true of our estimations of toxin in the faeces of these patients, though with one exception (case 16) all of those with detectable faecal toxin were severely ill. Five non-cytotoxic strains of *Cl difficile* were isolated; four were associated with diarrhoea in patients from whom no other presumptive pathogen was isolated. Pathogens other than *Cl difficile* were isolated from two severely ill patients (cases 7 and 8). One of these (case 7) had an associated salmonella bacteraemia, and presented with septicaemic shock initially considered to be secondary to an *Escherichia coli* urinary tract infection. With the exception of these two patients, 12 had a clinically severe illness in the absence of any presumptive cause other than *Cl difficile*. Seven of the 12 had received antibiotics within the previous six weeks, but the other five patients had not received antibiotics.

Management—Vancomycin was given to 10 of the 12 patients with clinically severe and moderately severe disease and to one patient with moderate disease. The decision to treat was clinical, though it was influenced by finding *Cl difficile* in the stools. At the time of each patient's illness we did not have the results of the faecal toxin assays; in retrospect it could be argued that several of our patients did not merit specific treatment. Cholestyramine was used only twice; it failed to improve one patient (case 12), who eventually received a course of vancomycin.

Sigmoidoscopy was performed on 11 patients (cases 1-8 and 10-12). Moderate inflammation with contact bleeding was seen in four (cases 1, 3, 7, and 8), but none had pseudomembranes or ulcers; the rest were normal. Rectal biopsy in six patients (cases 1, 3, 5, 6, 7, and 8) showed oedema with chronic or acute inflammatory infiltrates. Barium enemas were performed on two patients, and one showed severe diverticulosis.

Discussion

In a recent survey[5] no *Cl difficile* was isolated from a group of 62 healthy adults, but in an earlier one up to 3% of healthy adults were found to be carrying *Cl difficile*.[6] Most of this work, however, was done before the introduction of the selective CCFA medium.[2] Hence these surveys may have underestimated the carriage rate of *Cl difficile* if some normal adults had carried small numbers of organisms in their stools. Similarly, in our 35 controls we were unable to isolate any *Cl difficile* on CCFA. *Cl difficile* has been isolated from the urogenital tract of men and women,[7] occurs commonly in the faeces of neonates,[5 8] and has an accepted causative association with pseudomembranous colitis in adults. The organism has been associated with 6-48% of cases of antibiotic-associated diarrhoea[9-11]; the assumed association is based on faecal cytotoxin assays or isolations of the organism on selected media. Twelve of our 29 patients with antibiotic-associated diarrhoea yielded *Cl difficile*, but none had pseudomembranous colitis diagnosed. Mogg *et al*[12] and Keighley *et al*[13] have demonstrated the inadequacy of sigmoidoscopy and rectal biopsy and the greater reliability of faecal cytotoxin determinations in diagnosing pseudomembranous colitis.

Evidence is now appearing implicating *Cl difficile* in non-antibiotic-associated colitis,[14-16] exacerbations of chronic inflammatory bowel disease,[17 18] and postoperative diarrhoea.[10 13] The clustering of some cases suggests that cross-infection may occur.[19]

Falsen *et al*[11] found that *Cl difficile* was the second commonest enteropathogenic isolate in a survey of many stool specimens submitted to a laboratory. Our hospital-based survey would have excluded many young patients with salmonella and campylobacter infections treated by general practitioners without referral to hospital. In our series *Cl difficile* was the commonest presumptive enteric pathogen. Unknown or undetected pathogens might have accounted for some of our cases of presumed infective diarrhoea. For example, the occurrence of rotaviruses and other enteropathogenic viruses in an adult population has not been adequately assessed and merits further consideration. With these provisos, *Cl difficile* seems to be associated with some cases of diarrhoea requiring admission to hospital and may be acting as a primary pathogen in a proportion of these. In common with the findings of others,[11 20] we were able to isolate an accepted infective agent from only 28 (24%) of 115 patients. Our suggestion that *Cl difficile* may be an additional accepted cause of infective diarrhoea is supported by recent reports of hospital studies[19 21] and animal studies.[22 23]

The titres of faecal cytotoxin detected in our survey (from 0-1024) were appreciably lower than those obtained in classic cases of pseudomembranous colitis (500-400 000[24], 1000-5000,[25] and 1000-2000[26]). Our patients may have had illnesses at the lower end of the range of clinical severity. The *Cl difficile* isolates from five of our patients were non-cytotoxigenic, which raises the question whether non-cytotoxigenic *Cl difficile* is invariably non-pathogenic. Recent work suggests that the cytotoxin presently assayed is not the enterotoxin that causes the diarrhoea.[27]

When *Cl difficile* was isolated, a decision to treat was made on clinical grounds with oral vancomycin[28] or with cholestyramine.[29] That non-cytotoxigenic strains of *Cl difficile* might be implicated in diarrhoea led us to regard vancomycin as the first choice when specific treatment seemed to be indicated. The criteria required to implicate *Cl difficile* as an enteric pathogen are not yet clear. It may be helpful to avoid the terms toxigenic and non-toxigenic until the role of the cytotoxin and enterotoxin in relation to enterotoxicity is defined. It is important to determine whether a relation might exist between the numbers of organisms excreted, their ability to produce one or more toxic factors, the concentrations of these factors in the faeces, and the clinical condition of the patient. The epidemiology is complex,[30] and the enteropathogenic range of *Cl difficile* is as yet undefined. We suggest that the range of illness produced by *Cl difficile* may include sporadic infective diarrhoea and that oral vancomycin should be considered for patients whose clinical condition causes anxiety.

We thank Dr Margaret Calder and the staff of the City Hospital's bacteriology department, Dr Hamish Inglis and his colleagues at the Regional Virus Laboratory, and Professor Sir Alastair Currie and his staff at the University Department of Pathology for their help; the nursing staff of wards 16 and 16A without whose help we could not have organised and collected the specimens; Mr Garry Hay for technical work; Upjohn Ltd for financial support, equipment, and help with references; the Scottish Home and Health Department (Grant No K/MRS/50/C247) for the financial support of Dr I R

Poxton; and Mrs J Collins for typing the manuscript. Antitoxin for neutralisation tests was obtained from Dr P D Walker, of Wellcome Research Laboratories, Beckenham.

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(*Accepted 2 October 1981*)

SHORT REPORTS

Discharge of preterm babies from neonatal units

Until 1978 very low-birthweight (< 1500 g) and very preterm babies in our neonatal unit had to reach 2200 g before being discharged home. A controlled trial, however, showed that provided conditions at home were satisfactory and the babies were well and passsd the nadir of postnatal weight loss they could be discharged whatever their weight.[1] This confirmed observations in other countries.[2 3]

Such weight criteria, however, are still widely used in Britain, and we therefore report our experience.

Methods and results

From January 1978 to June 1980, 103 babies of 32 weeks' gestation or less or under 1500 g at birth were discharged home when clinically well, passed the nadir of postnatal weight loss, and feeding satisfactorily; home conditions were satisfactory; and the parents wanted the baby home. After discharge they were brought regularly for follow-up. We present information up to six months beyond their corrected age of term.

Weights of the babies at discharge ranged from 1300 to 3400 g (mean 1830 g). Average stay in hospital was five weeks (range three to seven). Of the 103 babies, 88 were discharged weighing under 2200 g, and 13 weighed 1500 g or less: half of these were "light for dates." Fifteen were discharged weighing 2200 g or more, most of these delays resulting from social problems —mother subnormal, mother in hospital, etc. Eleven babies were readmitted during follow-up (table). Only one weighed less than 2200 g, admission being for a transfusion for anaemia. Except for one baby with failure to thrive, all had gained weight satisfactorily. None of the others would have avoided readmission had they remained in hospital till reaching 2200 g. Readmissions were unrelated to early discharge.

Babies discharged from neonatal unit and needing admission to hospital six to nine months after delivery

No of babies	Reason for admission	Place of admission
1	Bronchitis	Children's ward
3	Repair of inguinal hernia	Neonatal unit
1	"Top-up" transfusion for anaemia	Neonatal unit
1	Suspected non-accidental injury	Neonatal unit
1	Confirmed non-accidental injury	Children's ward
1	Enucleation of left eye (planned admission)	Children's ward
2	Investigation of congenital heart disease	Children's ward
1	Failure to thrive	Children's ward

Comment

Delaying discharge of small babies from neonatal units until they reach a certain weight is difficult to justify. Health, progress, and home conditions should be the essential determinants. Success depends on helping the parents form the bond with the baby which would have developed had separation not been enforced. On admission to the unit a photograph of the baby is taken for the mother to keep at her bedside. The mother is visited regularly, and as soon as she is well enough encouraged to see her baby frequently. Brothers and sisters are also encouraged to visit. For two years wearing gowns has been abandoned, with no increase in infection.

The emphasis is on a relaxed environment and helping the parents look after their baby as soon and completely as possible. Physical contact is encouraged at an early stage—cleaning the baby's mouth, changing napkins, tube feeding, etc. Generally the earlier a bond is forged the more often will the parents visit. Participation continues as the baby progresses—bathing, feeding, making up feeds, choosing clothes. Babies are encouraged to pass as quickly as possible to breast