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Clostridium difficile-associated diarrhoea

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Summary

At our hospital, the number of cases of *Clostridium difficile*-associated diarrhoea increased from 29 in 1993 to 210 in 1995. The case notes of 110 patients with *C difficile*-associated diarrhoea during the first 6 months of 1995 were analysed retrospectively. The majority of the patients (106) had received antibiotics before the onset of diarrhoea; 46 had received three or more different antibiotics and 28 had received metronidazole. In 19 patients, the first stool sample after the onset of diarrhoea was negative for *C difficile* cytotoxin, with a mean delay of 8.2 days before a positive stool sample. We conclude that *C difficile*-associated diarrhoea was associated with the usage of multiple antibiotics, and that metronidazole did not protect against colonisation by *C difficile*. We also recommend that more than one stool sample should be tested for the *C difficile* cytotoxin.

Keywords: *Clostridium difficile*; diarrhoea; metronidazole

Clostridium difficile is a Gram-positive anaerobic bacillus that is the most commonly encountered bacterial enteropathogen in hospitalised patients. Infection caused by *C difficile* is an increasing problem as illustrated by a marked increase in the number of reported cases in England and Wales over the last 6 years.¹ At our hospital, the number of cases of *C difficile*-associated diarrhoea (CDAD) has increased from 29 in 1993 to 210 cases in 1995. To investigate this further, we have analysed the case notes of 110 patients with CDAD that occurred in 1995.

Methods

Hospital in-patients were identified from records in the microbiology laboratory of all stool samples received between 1 January and 30 June 1995 that were positive for *C difficile* cytotoxin (detected by standard Vero cell assay). The case notes of the identified patients were retrieved for detailed review. Information was recorded on patient demographics, antibiotic usage, investigations and treatment of CDAD, and outcome. Information on antibiotic usage prior to hospital admission was obtained from the patients' general practitioners.

Results

Out of 126 adult patients with CDAD, case notes were available for 110 (87.5%). Most of the patients were elderly, with a median age of 83 years (range 19-98; 53 male, 57 female) and the majority (73.7%) had been nursed on Health Care of the Elderly wards.

Of the 110 patients, 106 (96%) had received antibiotics prior to the onset of CDAD (table). Amongst these patients the use of multiple antibiotics was common, with 81 (76%) receiving two or more and 46 (43%) receiving three or more antibiotics prior to the onset of CDAD. Twenty-eight (26%) patients on antibiotics had received metronidazole, including

Table Antibiotic intake by patients prior to the onset of CDAD, including co-administration of metronidazole. Many patients received more than one antibiotic

Antibiotic	Number of patients taking each antibiotic (%)	Number of patients also taking metronidazole (%)
Cephalosporin*	81 (76)	23 (28)
Co-amoxiclav	26 (25)	7 (27)
Ampicillin/amoxycillin	28 (26)	3 (11)
Erythromycin	24 (23)	3 (13)
Trimethoprim	17 (16)	5 (29)
Flucloxacillin	14 (13)	6 (43)
Ciprofloxacin/ofloxacin	10 (9)	1 (10)
Gentamicin	6 (6)	2 (33)
Clarithromycin	2 (2)	2 (100)
Penicillin V	2 (2)	0 (0)
Rifampicin	1 (1)	1 (100)
Teicoplanin	1 (1)	0 (0)
Clindamycin	1 (1)	0 (0)

*cefotaxime, cefuroxime, ceftazidime or cephradine

nine (8%) who were on it at the onset of CDAD. Only seven patients had not received a broad-spectrum antibiotic prior to the onset of CDAD. They included two on clarithromycin (both also on metronidazole), two on trimethoprim alone and one each on trimethoprim and ofloxacin, ciprofloxacin, or flucloxacillin. Four patients did not receive any antibiotics in hospital prior to the onset of CDAD and review of their general practitioner records revealed that three had not received any antibiotics in the preceding 12 months.

The median (range) interval between the day of admission and the onset of diarrhoea was 19.4 days (1–151). In 19 (17%) patients the first stool sample after the onset of diarrhoea was negative for the cytotoxin, with a mean ($\pm$ SD) delay of 8.2 ($\pm$ 6.6) days before a positive stool sample (second sample in all cases). The median (range) duration of hospital stay for all patients with CDAD was 42 days (12–269) days. Fifty-one (46%) patients died in hospital.

Discussion

C. difficile infection is an increasing problem in hospitalised patients. Elderly patients on antibiotics, particularly cephalosporin and broad-spectrum penicillin, appear to be particularly susceptible.² Our study has shown that the majority of patients had received two or more different antibiotics prior to the onset of CDAD. Colonisation with *C. difficile* occurs following disruption of the normal colonic flora by antibiotics³ and our studies suggest that multiple antibiotics may increase the risk of infection due to a greater degree of disruption of the microflora. However, three patients with CDAD had not received any antibiotic for at least 12 months prior to the onset of diarrhoea, suggesting a role for other factors in disruption of the normal colonic flora. The only other drugs that these three patients had received were antihypertensive drugs (angiotensin-converting enzyme inhibitors and diuretics) and/or bronchodilators (including inhaled corticosteroids).

Metronidazole and vancomycin have been reported to be equally efficacious in the treatment of *C. difficile*-associated disease.⁴ We were therefore surprised to find that 26.4% of patients had received metronidazole prior to

the onset of CDAD, including 8% who were on the drug at the time of the onset of diarrhoea. Although there are reports of CDAD associated with the ingestion of metronidazole,⁵ we believe this is the first report of such a large number of patients who developed CDAD after receiving metronidazole. All the patients on metronidazole were also taking other antibiotics, including two on clarithromycin. We have recently also managed a 79-year-old patient who developed pseudomembranous colitis (*C. difficile* toxin positive) in the community while taking omeprazole, amoxycillin and metronidazole for eradication of *Helicobacter pylori*. Since metronidazole and clarithromycin or amoxycillin, together with potent acid suppression, are frequently used to eradicate *H. pylori*,⁶ use of this combination of drugs in the elderly may predispose to CDAD. A possible explanation for the failure of metronidazole to protect against colonisation by *C. difficile* is that inadequate levels of the drug were achieved in the colonic lumen of these patients.

Another important aspect of our study is the finding that in 17% of patients, analysis of the first stool sample was negative for *C. difficile* cytotoxin. It is possible that, at the time the first (negative) stool sample was obtained, the patients were not colonised with toxigenic *C. difficile* but had acquired the organism by the time the second (positive) stool sample was taken. However, since the patients had diarrhoea on both occasions (and also in the intervening period), we believe the more likely explanation is that the first stool sample was falsely negative for *C. difficile* cytotoxin. Appreciation of this possibility is important in clinical practice as there was a mean delay of 8.2 days before a cytotoxin-positive stool sample was reported, leading to a delay in the institution of appropriate treatment. The assay used for the detection of *C. difficile* toxin is based on the demonstration of cytotoxicity in a mammalian cell line and is considered to be the gold standard.⁷ Early sigmoidoscopic examination in patients with significant diarrhoea may show the presence of mucosal inflammation, with characteristic histological appearances on biopsy,⁸ and is likely to be helpful in the early diagnosis and assessment of patients with CDAD.

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