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Antibiotic prescribing policy and *Clostridium difficile* diarrhoea

K.A. O'CONNOR, M. KINGSTON, M. O'DONOVAN, B. CRYAN[1], C. TWOMEY and D. O'MAHONY

From the South Munster Geriatric Training Scheme, Departments of Geriatric Medicine and [1]Microbiology, Cork University Hospital, Cork, and St. Finbarr's Hospital, Cork, Ireland

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Summary

Background: Broad-spectrum antibiotics, particularly intravenous cephalosporins, are associated with *Clostridium difficile* diarrhoea. Diarrhoea due to *C. difficile* is a growing problem in hospitals, especially among elderly patients.
Aim: To establish whether changing an antibiotic policy with the aim of reducing the use of injectable cephalosporins leads to a reduction in the incidence of *C. difficile* diarrhoea in elderly patients.
Design: Retrospective analysis.
Methods: A group of patients who were subject to the new antibiotic policy from the period following July 2000, were compared with patients who were admitted prior to July 2000 and were not subject to the new policy. Infections, antibiotic prescriptions and mortality rates were determined from case notes, and *C. difficle* diarrhoea rates from microbiological data.
Results: Intravenous cephalosporin use fell from 210 to 28 defined daily doses ($p<0.001$) following the change in antibiotic policy, with a corresponding increase in piperacillin-tazobactam ($p<0.001$) and moxifloxacin ($p<0.001$) use. The new policy led to a significant reduction in *C. difficile* diarrhoea cases. The relative risk of developing *C. difficile* infection with the old policy compared to the new policy was 3.24 (95%CI 1.07–9.84, $p=0.03$).
Discussion: The antibiotic policy was successfully introduced into an elderly care service. It reduced both intravenous cephalosporin use and *C. difficile* diarrhoea.

Introduction

Clostridium difficile diarrhoea is an increasing problem, particularly in elderly hospitalized patients.[1,2] In England and Wales, the number of laboratory reports of detection of *C. difficile* or its toxins increased about four-fold in the 1990s.[1] Antibiotic exposure is the chief risk factor for this disease,[3,4] and almost any antibiotic may predispose to *C. difficile* infection. A prolonged course of antibiotics or the use of two or more antibiotics in combination increases the risk of *C. difficile* diarrhoea.[5] However, even brief exposure to a single dose for surgical prophylaxis can precipitate diarrhoea.[6] Despite stringent infection control measures, our health region was experiencing an increasing incidence of *C. difficile* infection (Figure 1). Mirroring the UK experience,[1] geriatric units in the region were suffering most of the increase.

In current practice, broad-spectrum penicillins and cephalosporins are the main cause of *C. difficile* diarrhoea, reflecting their widespread use. Intravenous third-generation cephalosporins represent the highest risk for antibiotic-associated diarrhoea,[7,8] and the incidence of *C. difficile* diarrhoea

Address correspondence to: Dr D. O' Mahony, Department of Geriatric Medicine, Cork University Hospital, Wilton, Cork, Ireland. e-mail: omahonyd@shb.ie

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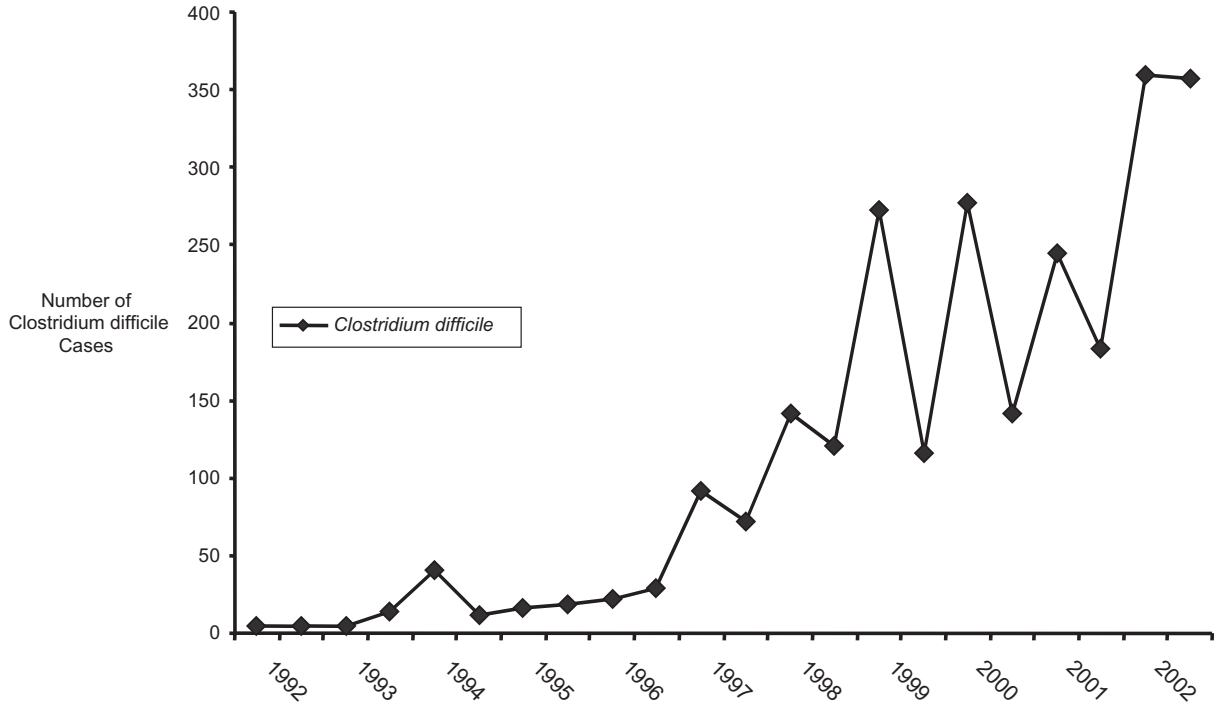

Figure 1. Trend in *C. difficile* toxin-positive cases in the Munster region 1992–2002. Data on file at Microbiology Laboratory Cork University Hospital.

is closely linked to cephalosporin usage.[9] Therefore, in July 2000 our antibiotic policy was reviewed, and changes restricting indications for all intravenous cephalosporin use were introduced. The main alterations were in the recommended treatments for lower respiratory tract infections. Piperacillin-tazobactam was introduced as a broad-spectrum intravenous preparation, and moxifloxacin, an 8-methoxyquinolone, as an oral alternative. It was hypothesized that these agents would have a reduced propensity to cause *C. difficile* diarrhoea. Despite their broad spectrum of activity, the anti-pseudomonal penicillins, such as piperacillin-tazobactam, carry a reduced risk of *C. difficile* diarrhoea compared to intravenous cephalosporins.[7,10,11] Moxifloxacin is characterized by high activity against Gram-positive cocci and some Gram-positive and -negative anaerobes, including *C. difficile*.[12–15]

It remains to be seen whether the *in vitro* activity of new fluoroquinolones, such as moxifloxacin, against *C. difficile*[14,15] results in a reduced occurrence of *C. difficile* infection. To date there have been no clinical trials that examine the role of moxifloxacin use in reducing *C. difficile* diarrhoea. In this study, we tested whether a new antibiotic prescribing policy that was aimed at restricting the use of intravenous cephalosporins could successfully be introduced to an elderly care service, and whether the use of moxifloxacin and piperacillin-tazobactam as alternatives resulted in a reduced occurrence of *C. difficile* diarrhoea.

Methods

Antibiotic policy

In conjunction with the hospital's microbiology department, the acute care unit and rehabilitation wards of the elderly care service implemented a new antibiotic policy in July 2000. For many years, the unit policy had recommended the use of narrow-spectrum antimicrobials targeted to the site of infection. However, the third-generation cephalosporin ceftriaxone was recommended for some hospital-acquired infections. In July 2000, in the light of increasing numbers of cases of *C. difficile* diarrhoea, restrictions were made on the indications for third-generation cephalosporins. Ceftriaxone was the only intravenous third-generation cephalosporin in use in the department throughout the study period. As a principle of the new policy, the use of all intravenous second- and third-generation cephalosporins was discouraged if alternatives were available.

The main changes were in the treatment of respiratory infections. Co-amoxiclav was once again recommended as first line for community-acquired pneumonia. For hospital-acquired pneumonia,

Table 1 Antibiotic prescribing policy for respiratory tract infections

Type of infection	Old policy	New policy
Community-acquired pneumonia: non-severe	Co-amoxiclav p.o or i.v.	Co-amoxiclav p.o or i.v.
	Or	Or
	Clarithromycin (if penicillin-allergic)	Clarithromycin (if penicillin-allergic)
Community-acquired pneumonia: severe	Ceftriaxone i.v.	Ciprofloxacin i.v. plus benzylpenicillin
	Or	Or
	Ciprofloxacin i.v. plus clarithromycin (if penicillin-allergic)	Ciprofloxacin i.v. plus clarithromycin (if penicillin-allergic)
Hospital-acquired pneumonia: non-severe	Ceftriaxone i.v.	Moxifloxacin p.o.
Hospital-acquired pneumonia: severe	Ceftriaxone i.v. plus gentamicin i.v.	Piperacillin-tazobactam i.v. plus clarithromycin (if not responding)
Aspiration pneumonia	Cefuroxime i.v. plus metronidazole i.v.	Piperacillin-tazobactam i.v.
		Or
		Metronidazole plus clarithromycin (if penicillin-allergic)
Atypical pneumonia	Clarithromycin	Clarithromycin

oral moxifloxacin was recommended, or in cases of severe pneumonia intravenous piperacillin-tazobactam was the antibiotic of choice (Table 1). For urinary tract infections, cefuroxime, one of the previously recommended first-line agents, was now omitted. Co-amoxiclav or trimethoprim were recommended as initial treatment in suspected urinary tract infections until culture and sensitivity results were available. The new policy was part of the unit policy document portfolio. All new staff members obtained a copy of the unit policy portfolio on rotation to the elderly care services, and at an introductory presentation on all unit policies. Discussion at multidisciplinary team meetings and feedback at the monthly departmental audit meeting further promoted the new antibiotic policy.

Patients

All patients were aged 65 years and over. We studied patients in two 4-month periods: one before (1 January 2000 to 30 April 2000) and one after (1 January 2001 to 30 April 2001) the change in antibiotic policy. All patients were admitted to a 25-bed acute geriatric unit with a heterogeneous, unselected variety of medical conditions. Rehabilitation after acute illness was provided in an off-site 80-bed rehabilitation unit. All admissions to the rehabilitation unit were first assessed in the acute geriatric unit. Within the acute admission unit, the majority of elderly patients were nursed in 6-bed bays with shared toilet facilities. Four single rooms with en suite toilet were available for patient isolation if necessary. In the rehabilitation unit, there were two 40-bed wards, each with six 6-bed bays—each bay had a separate shared toilet facility. Each rehabilitation ward had four single rooms for patient isolation where necessary.

Infection control

Hospital policy is to isolate all cases of *C. difficile* diarrhoea in single rooms with en suite toilet and washing facilities. Gloves and aprons were worn when handling the patient, and ward transfer was avoided until diarrhoea had settled. Infection control policy did not change during the time period of this study.

Microbiology

The microbiology department has a standard operational procedure for handling stool specimens, which remained unchanged over the time-period

of this study. Stool samples from all patients were cultured for the usual bacterial pathogens (*Salmonella, Campylobacter, Shigella*). All specimens from patients with liquid or bloody diarrhoea or specimens from patients receiving or recently finished antibiotics were tested for *C. difficile* toxins. *C. difficile* toxins A and B were detected using an enzyme immunoassay—*C. difficile* TOX A/B (Techlab).[16] The department of microbiology maintains an independent record of all *C. difficile* toxin tests. This record was reviewed in order to identify all cases of proven *C. difficle* diarrhoea during the study period.

Admission details

In order to avoid possible confounding from increased vigilance in the first 6 months of implementing the new policy, only data relating to patients hospitalized 7–11 months after the policy introduction (1 January 2001 to 30 April 2001) were collected. These data were compared to a similar period prior to implementing the new policy (1 January 2000 to 30 April 2000). Details of all admissions to the elderly care service were collected from the two 4-month periods. Of the total patients' case-notes, 96.8% in the first period and 97.9% in the second period were available for retrospective review. All drug prescriptions were reviewed for each admission, and any instance of antibiotic prescription was identified. The dose of antibiotic and length of treatment were recorded for each prescription. All admissions with infection as a primary or secondary diagnosis were identified. Infections were then grouped into respiratory, urinary or 'other'. In all cases of a *C. difficile* toxin-positive result as identified from microbiology data, case-notes were used to confirm the presence of diarrhoea.

Statistics

The number of defined daily doses (DDD) for each antibiotic was calculated from the antibiotic doses and lengths of treatment.[17] The number of defined daily doses was used for subsequent analysis. All statistical analysis was performed with Stata for Windows software (Version 7.0). Baseline summary statistics are reported as means ± SD for continuous variables and as numbers (%) for categorical variables. Age as a continuous variable was analysed using the *t*-test. Statistical comparisons of the categorical variables were made using the χ^2 test and Fisher's exact test. All tests were two-tailed. $p < 0.05$ was taken as significant. The relative risk and 95%CI for developing toxin-positive *C. difficile* diarrhoea between the two policy periods were also calculated.

Results

During the respective periods studied, before and after the change in antibiotic policy, there were 344 and 339 admissions to the acute geriatric care unit. The proportions of case-notes that were available for review were not significantly different (96.8% vs. 97.9% respectively). The gender breakdown and mean age was similar in both groups (Table 2). The diagnosis of infection, both as a primary cause

Table 2 Baseline characteristics, infective episodes, mortality rates and *C. difficile* cases

	Old policy* ($n = 333$)	New policy* ($n = 332$)	*p*
Age (mean ± SD)	82.3 ± 6.9	83.1 ± 7.1	0.34
Male (%)	166 (48.3%)	159 (46.9%)	0.61
Overall mortality (%)	77 (22.4%)	79 (23.3%)	0.84
Primary infection	115	108	0.98
Number of patients with secondary infection**	57	66	0.36
Number of patients with respiratory infection***	73	74	0.91
Number of patients with urinary infection***	60	56	0.70
Number of patients with other infections***	31	30	0.90
Mortality in respiratory group (%)	28 (38.4%)	27 (36.5%)	0.90
Mortality in urinary group (%)	10 (16.7%)	12 (21.4%)	0.66
Mortality in other group (%)	5 (16.1%)	8 (26.7%)	0.40
C. difficile toxin-positive	13	4	0.03

* Data based on available case-notes, 96.8% of old policy and 97.9% new policy of admissions. ** Includes patients with both primary and secondary infections (old policy, $n = 31$, new policy $n = 37$). *** Some patients counted for more than one infective diagnosis, as different infections occurred at different stages of admission.

of admission or as a secondary phenomenon in hospital, showed no significant difference with the introduction of the revised antibiotic policy (Table 2). The types of infection diagnosed (respiratory, urinary or other infection) were also similar before and after the antibiotic change (Table 2). There were no changes in the case-mix of admissions to the unit between the periods studied. There were 141 patients (41.0%) with some form of infection during their admission in the initial period studied and a similar number, 137 patients (40.4%), in the second study period ($p=0.78$). For all infections, the mortality rates were 26.9% and 30.7%, respectively ($p=0.49$), with no significant difference in the mortality rates for the three infection groups between the two periods (Table 2).

Following the change in antibiotic policy, there were highly significant reductions in the use of intravenous cephalosporins, with a corresponding increase in the use of piperacillin-tazobactam and moxifloxacin (Table 3). The use of intravenous cefuroxime was completely eliminated. The use of oral cefuroxime was reduced from 70 DDD to 49 DDD ($p=0.08$). As expected, the numbers of prescriptions for co-amoxiclav were similar between both study periods, given that indications for co-amoxiclav did not change. With the use of cefuroxime discouraged for urinary tract infections, the use of trimethoprim (25 DDD vs. 41 DDD, $p=0.06$) and nitrofurantoin (50 DDD vs. 68 DDD, $p=0.14$) increased. Overall antibiotic use was similar before and after the change in policy (1008 DDD vs. 998 DDD, respectively, $p=0.95$).

In the period before and after the policy change there were similar numbers of stool cultures for *C. difficile* sent to the laboratory from the elderly care wards (66 vs. 78, $p=0.36$). However, there was a significant reduction in the number of patients found to have *C. difficile* toxin-positive diarrhoea following the introduction of the new policy (Table 2). All of the 17 cases of toxin-positive *C. difficile* diarrhoea (13 cases with the old policy and 4 with the new, $p=0.03$) were treated with antibiotics for respiratory tract infections. Of the four cases with the new policy, one had a single prescription for antibiotics, another one had two prescriptions for antibiotics and two had three prescriptions. Three of these patients, including the case with a single antibiotic prescription, were prescribed a cephalosporin. Six of the 13 patients that developed *C. difficile* diarrhoea with the old policy had only a single prescription for antibiotics, and nine cases (69.2%) were prescribed a cephalosporin. All cases of *C. difficile* diarrhoea were nosocomially acquired. The relative risk of developing *C. difficile* diarrhoea with the old policy compared to the new antibiotic policy was 3.24 (95%CI 1.07–9.84, $p=0.03$). The attack rate for *C. difficile* diarrhoea per 100 antibiotic DDD fell from 1.3 to 0.4 following the change in policy.

Table 3 Number of defined daily doses of antibiotics

	Old policy	New policy	*p*
Ceftriaxone disodium (i.v.)	118	28	<0.001
Cefuroxime disodium (i.v.)	92	0	<0.001
Piperacillin-tazobactam	17	123	<0.001
Co-amoxiclav	231	211	0.48
Moxifloxacin	0	104	<0.001
Cefuroxime axitel (oral)	70	49	0.08
Clarithromycin	166	138	0.20
Ciprofloxacin	72	66	0.65
Nitrofurantoin	50	68	0.14
Trimethoprim	25	41	0.06
Metronidazole	104	88	0.32
Other antibiotics	63	82	*

* There was no significant difference for any other individual antibiotic.

Discussion

The introduction of the new antibiotic policy had the desired effect of significantly reducing the use of intravenous cephalosporins. The reduction in intravenous cephalosporin use was accompanied by a corresponding increase in the use of the two new drugs to the antibiotic prescribing policy—piperacillin-tazobactam and moxifloxacin. The patient groups were well matched in all respects other than the antibiotics used to treat their infections. There was a similar breakdown in the infective diagnosis in both study periods. There was no change in laboratory testing methods during the study period. The concern that introducing a new antibiotic policy may increase mortality by not providing adequate cover against resistant pathogens proved unfounded in this study. The number of cases of proven *C. difficile* toxin-positive diarrhoea was significantly reduced to less than one-third of the number of cases occurring with the old antibiotic policy.

The major limiting factor in this study is the retrospective design, with a historical cohort used as the control group. At the time of the study there was mounting evidence that piperacillin-tazobactam did not carry the same risk of *C. difficile* diarrhoea as intravenous cephalosporins.[8,10,11] For this reason, it was deemed unethical to limit

treatment with piperacillin-tazobactam as would have been needed for a prospective study. The problem of *C. difficile* diarrhoea had continued to rise in the region over the previous 10 years (Figure 1), and our control group was representative of this increasing incidence. However, the overall number of cases in the first half of 2001 in the region is lower than the corresponding period of the previous year. This drop is almost exclusively accounted for by a reduction in *C. difficile* cases in the elderly care units of our hospital, and the number of cases in the other major hospitals in the region continued to climb in 2001. Unfortunately, there were supply difficulties with pipercillin-tazobactam from late 2001 and throughout 2002. Despite the temporary improvement in *C. difficile* numbers in 2001, the trend in the region was reversed in 2002 (Figure 1).

The primary aim of this study was to examine if a new antibiotic policy aimed at limiting intravenous cephalosporin use could be successfully introduced on the basis of recommending pipercillin-tazobactam and moxifloxacin as alternatives. In our view, a retrospective design still gives appropriate results, as prospective monitoring of the policy as part of an on-going clinical trial would have influenced the choice of antibiotics used. A reduction in intravenous cephalosporin use was successfully accomplished in this study. This was a key objective, since cephalosporins are now recognized as the major cause of *C. difficile* diarrhoea[4,7,8,18–20] and elderly patients, as in this study, are the most susceptible to *C. difficile* diarrhoea. Strict infection control policies were in place prior to revising the unit's antibiotic policy; these alone were not adequate in controlling *C. difficile* outbreaks. The substitution of piperacillin-tazobactam and moxifloxacin for cephalosporins in respiratory disease adds to the previously proven antibiotic alternatives.[9,11,21] Despite the principle of using alternatives to cephalosporins, it was not feasible or perhaps appropriate to eliminate their use altogether. Not surprisingly, three of the four cases of *C. difficile* diarrhoea with the new policy had taken a cephalosporin. Reasons for difficulty implementing change are multiple but include: staff turnover; out-of-hours cross-covering of staff; penicillin allergy; difficulty in establishing the source of infection in elderly patients; and fear of inadequate antibiotic treatment without a third-generation cephalosporin. Cost is also an important consideration when revising prescribing policies, particularly when advocating expensive antibiotics such as the anti-pseudomonal penicillins. Previous studies have demonstrated that the increased cost of these antibiotics can be offset by the saving in reduced mortality, morbidity and bed occupancy that result from controlling *C. difficile*.[11,21–23] In 1996, the additional cost of a *C. difficile* diarrhoea case had been shown to be >£4000.[22] Even though we did not demonstrate a complete elimination of intravenous cephalosporin use, we did show significant reductions, and the policy change resulted in significant reductions in *C. difficile* diarrhoea cases.

The fact that this study resulted in a number of antibiotic changes makes it difficult to establish a direct cause and effect for an individual antibiotic. Unlike some previous work, we examined a complete antibiotic policy and its effect on *C. difficile* rather than the effect of an individual drug. This study corroborates previous work advocating pipercillin-tazobactam as a substitute for cephalosporins with a reduced risk of *C. difficile* cases.[9–11,21,24] Two previous studies succeeded in reducing *C. difficile* diarrhoea incidence by restricting access to cefuroxime,[9,24] and interestingly, we observed a complete elimination of intravenous cefuroxime use in this study. This is the first clinical study that indicates that the substitution of the quinolone moxifloxacin is associated with a reduced infection rate from *C. difficile.* Moxifloxacin, approved by the Food and Drug Administration in 1999, was available only as an oral preparation at the time of the study. It shows a high level of activity against many anaerobes, including *C. difficile*.[12–14] This activity, and its convenient once daily dosing, make it an interesting prospect for use in elderly care units where *C. difficile* is endemic. However, in the past year there have been reports of moxifloxacin-induced *C. difficile* diarrhoea.[25,26] It would also seem that there is increasing resistance to moxifloxacin in *C. difficile* isolates.[27] Clinical use of new generation fluoroquinolones in elderly hospitalized patients in order to reduce *C. difficile* cases is an interesting development, with a recently reported study also showing that another fluoroquinolone, levofloxacin, substituting for ceftriaxone reduces the incidence of *C. difficile*-associated diarrhoea.[28]

In conclusion, an antibiotic policy aimed at reducing the use of intravenous cephalosporins can be successfully introduced in an elderly care service without increasing the mortality rate. The combination of reduced intravenous cephalosporin use in association with increased piperacillin-tazobactam and moxifloxacin use led to a significant reduction in *C. difficile* diarrhoea infection in elderly patients. Judicious antibiotic prescribing and stringent infection control measures must still be part of the standard approach to preventing *C. difficile* diarrhoea. However, when empirical broad-spectrum antibiotics are required in elderly

patients, piperacillin-tazobactam is a better choice than third-generation cephalosporins, because of the lower risk of morbidity secondary to *C. difficile* diarrhoea. Clinical use of new generation fluoroquinolones such as moxifloxacin in elderly hospitalized patients where *C. difficile* is highly prevalent, is an interesting new intervention that will require some further study. Antibiotic policies aimed at reducing the use of cephalosporins in elderly patients are worthy of consideration as a means of reducing the incidence of *C. difficile* diarrhoea.

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