Incidence of Antibiotic-Associated *C. difficile* Diarrhea in a Teaching Hospital

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ABSTRACT

The objective of this retrospective study was to determine the prevalence of antibiotic-associated Clostridium difficile diarrhea (CDD) in a teaching hospital for the year 1995. It was intended to establish the incidence of CDD for each etiological agent, taking into account the total number of patients treated with the agent at Laval Hospital over a period of 1 year. Using positive samples in a search for Clostridium difficile cytotoxin, a retrospective review of medical records was carried out in order to identify the antibiotics prescribed in the 2 months preceding the diagnosis. The pharmacy's computer software was then used to calculate the number of patients treated over a period of 1 year with each of the antibiotics listed in the hospital's drug formulary. Forty-two patients were diagnosed with CDD in 1995. Of this number, 23 patients had begun antibiotic treatment outside the hospital. For 6 of these 23 patients (17%), cefuroxime axetil was the causal agent. For those patients put on antibiotics when they were hospitalized, the calculated incidence was 1.8% for clindamycin, 0.8% for third generation cephalosporins IV, 0.5% for ciprofloxacin, and 0.5% for amoxicillin/ampicillin. The calculated incidence for cefuroxime among these patients was 0.4%. Nearly 80% of users received an association of antibiotics at the hospital, thus making any conclusion difficult in this context.

Key-words: antibiotherapy, *C. difficile* diarrhea, negative side-effect, pseudomembranous colitis.

RÉSUMÉ

Le sujet de cette étude rétrospective est de déterminer la prévalence de la diarrhée à Clostridium difficile (DCD) associée à l'antibiothérapie, dans un hôpital universitaire durant l'année 1995. L'étude vise à établir l'incidence de la DCD pour chacun des agents causals, en tenant compte du nombre total de patients traités par chaque agent à l'Hôpital Laval sur une période d'une année. Une analyse rétrospective des dossiers médicaux a été menée à partir d'échantillons positifs à la recherche de cytotoxine de Clostridium difficile, dans le but d'identifier les antibiotiques prescrits dans les deux mois précédant le diagnostic. Le logiciel de la pharmacie a par la suite été utilisé pour calculer le nombre de patients traités sur une année pour chacun des antibiotiques présents sur le formulaire des médicaments de l'hôpital. En 1995, la DCD a été diagnostiquée chez 52 patients. De ce nombre, 23 avaient amorcé une antibiothérapie à l'extérieur de l'hôpital. Chez six de ces 23 patients (17 %), le céfuroxime axétil était l'agent causal. Pour les patients qui ont reçu une antibiothérapie lors de leur hospitalisation, le taux d'incidence de la DCD calculé était de 1,8 % pour la clindamycine, de 0,8 % pour les céphalosporines de 3e génération par voie i.v., de 0,5 % pour la ciprofloxacine et de 0,5 % pour l'amoxicilline/ampicilline. Le taux d'incidence calculé pour le céfuroxime chez ces patients était de 0,4 %. Près de 80 % des patients ont reçu une association d'antibiotiques à l'hôpital, ce qui a rendu difficile toute conclusion dans ce contexte.

Mots clés : antibiothérapie, colite pseudomembraneuse, diarrhée à *C. difficile*, effets indésirables

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INTRODUCTION

Clostridium difficile diarrhea (CDD) is a gastrointestinal infection caused by a gram positive anaerobic spore-producing bacillus: *Clostridium difficile*.[1,2] This micro-organism produces two exotoxins: an enterotoxin or toxin A, and a cytotoxin or toxin B.[1-4] These are the toxins responsible for lesions in the colonic mucous membrane and for characteristic clinical signs of the disease.[5] Colonization may be without symptoms or cause slight or very severe diarrhea with or without abdominal cramps and fever.[2,3] The formation of plaques or pseudomembranes on the mucous membrane of the colon is not always seen.[2-4] The diagnosis of CDD is established from clinical symptoms and stool cultures. Colonoscopy is not usually necessary for the diagnosis but can be useful when the clinical presentation is sudden and severe and requires rapid diagnosis.[2,3]

The etiology of CDD is not yet fully understood. After colonization, in order for the infection to develop, there must be a prior disturbance in the balance of the normal intestinal flora.[2-5] With a large majority of patients, CDD is linked to the use of antibiotics, or more rarely, antineoplasics like methotrexate or 5-fluorouracil.[2,6] On the other hand, it is still not known why only some patients acquire the infection and others do not. Certain risk factors linked to

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the host have been identified: advanced age, severe disease, multiple antibiotics, surgery or recent gastrointestinal manipulations.[1,2] Hospitalization is also an important risk factor.[2] The incidence of the disease is much lower with ambulatory patients (1-2 cases/100, 000) than with those who are hospitalized (1-10 cases/1000).[7]

All antibiotics, especially those with a wide spectrum of effect on the anaerobic gastrointestinal flora, may be associated with CDD.[2,3] Antibiotics most frequently involved are clindamycin, ampicillin, amoxicillin, and cephalosporins.[2,3,6] Oral administration of the agent increases the risks as does the duration of the therapy.[1,7] On the other hand, cases of CDD have been reported in patients who received only one dose for surgical prophylaxis.[1,2,4] In the majority of cases, the antibiotic was currently being used or had just been stopped only a few days before the onset of symptoms.[3,6,8] A delay of up to 8 to 10 weeks is possible however, before clinical signs of the disease begin to manifest themselves.[1,2]

The growing use of cephalosporins in the treatment of low respiratory infections as well as association perceived by clinicians at our centre between cefuroxime and CDD led to this study being carried out. Its objectives are to establish the prevalence of cases of antibiotic-associated CDD in a teaching hospital for the year 1995, and to establish the incidence of CDD for each etiological agent taking into account the total number of patients at Laval Hospital who were treated with the agent over a period of 1 year.

METHODOLOGY

The study was carried out from January 1, 1995 to December 31, 1995 in a 350-bed tertiary care teaching hospital providing adult care in cardiology and respirology. This is a descriptive, retrospective study dealing with all the cases of CDD diagnosed during this period. Cases were identified from samples of stools testing positive for *Clostridium difficile* cytotoxin by the microbiology laboratory (Baxter Diagnostics Inc. B1029-70). This diagnostic method is based upon the presence of cytotoxin or toxin B in the stools. This is the standard method adopted over the last several years.[2,3,6,8] This is a highly specific method, but its sensitivity, although very good, is limited by the storage conditions of the sample, since the toxin is sensitive to heat.[2,4]

A retrospective review of medical records was carried out in order to identify the status of the patients at the time of diagnosis and the antibiotic(s) used in the 2 months preceding the diagnosis. It was also necessary to specify whether or not the antibiotic prescription originated from Laval Hospital.

In order to determine the incidence for each agent, a retrospective review of antibiotic use was carried out using computer software used for the distribution of medication. This program makes it possible to retrace for a given period all patients treated with specific medications determined beforehand. This review of antibiotic use dealt with the treatments begun between November 1, 1994 and December 31, 1995. All the treatments were compiled including those antibiotics given in prophylactic surgery.

RESULTS

A first diagnosis of CDD was made for 42 patients from January 1, 1995 to December 31, 1995. The average age was 59.3, 52.4% of the group was male. The status of the patients at the time of the first diagnosis of CDD is shown in Table I. CDD was the main cause of hospitalization for 11 patients. The average duration of the stay in hospital was 5.7 days for these patients. The average stay for patient who acquired CDD during hospitalization was 17.5 days after the diagnosis of CDD had been made.

Twenty-three patients were diagnosed with CDD associated with an out-patient antibiotic in the 2 months preceding the diagnosis (Table II). Of this number, it

Table I. Status of Patients at the Time of First Diagnosis of CDD* (N = 42)

Ambulatory:	9 (21.4 %)
Hospitalized:	33 (78.6 %)
Admission diagnosis	**Number (%)**
Other than CDD	19 (57.6)
CDD	11 (33.3)
CDD and other problems	3 (9.1)

*CDD denotes *C. Difficile* diarrhea

Table II. CDD Diagnosis Associated with Out-Patient Antibiotic (N = 23)

Antibiotic unspecified:	8 (34.8%)	
Antibiotic identified:	15 (65.2%)	
	Only AB* responsible (n = 12)	**In association (n = 3)**
Cefuroxime axetil	6	1
TMP / SMX	3	0
Amoxicillin	1	2
Cefixime	1	0
Doxycycline	1	0
Ciprofloxacin	0	1
Clindamycin	0	1

*AB denotes antibiotic

was impossible to determine precisely the nature of the agent used for 8 patients. For the other 15 patients, 12 received only 1 antibiotic while 3 were exposed to 2 antibiotics. The agent most frequently involved was cefuroxime axetil which accounts for half the cases linked to one antibiotic (6 of 12). TMP-SMX was associated with 3 cases. Amoxicillin, cefixime, and doxycycline were involved in the remaining 3 cases.

Table III shows the 22 cases of CDD associated with treatment begun during the current or previous hospitalization at Laval Hospital. An association with antibiotics was found in 17 patients (77.3%). A single causal agent was identified in 5 patients. Clindamycin was the antibiotic involved in 9 cases (41%), but always in association with another agent. For the other antibiotics, excluding the association with clindamycin, ciprofloxacin was the medication most frequently involved (5 cases). The other agents involved are detailed in Table III.

The incidence of CDD in patients having received antibiotic treatment at Laval Hospital in the year 1995 is shown in Table IV. The incidence was calculated using the number of cases reported when the antibiotic was the sole causal agent or when it was found in an association with another agent, excluding clindamycin (numerator) as a function of the number of treatments prescribed for a specific antibiotic from November 1, 1994 to December 31, 1995 (denominator). The highest incidences occurred with imipenem / cilastatin (3.4%) and clindamycin (1.8%). A group of cephalosporins including ceftazidime, ceftriaxone, and cefoxitin has a reported incidence of 0.8%. Ciprofloxacin, a group made up of ampicillin and amoxicillin, and amoxicillin / clavulanate each show an incidence of 0.5%.

Table III. CDD[1] Diagnosis Associated with Antibiotic Therapy Begun at Laval Hospital (N = 22)

	Only AB[2] Responsible (N = 5)*	Association with Clindamycin (N = 9)*	Association with an AB Other Than Clindamycin (n = 8)*
Clindamycin	0	-	9
Ciprofloxacin	2	7	3
Other penicillins**	1	3	4
Other cephalosporins***	0	2	4
Cefazolin / Cephalexin	0	1	4
Ampicillin / Amoxicillin	1	0	2
Cefuroxime	1	1	2
Metronidazole	0	0	2
Imipenem / Cilastatin	0	0	1
Amoxicillin / Clavulanate	0	1	1
Macrolides	0	1	1
Aminosides	0	3	0

* Only 1 AB involved: 5 (22,7%)
2 ABs involved: 4 (18,2%)
3 ABs or more: 13 (59,1%)
** Cloxacillin / Penicillin G / Ticarcillin / Piperacillin
*** Ceftazidime / Ceftriaxone / Cefoxitin
1. CDD denotes *C. Difficile* diarrhea
2. AB denotes antibiotic

Table IV. Incidence of CDD[1] for Patients Who Received Antibiotic Treatment at Laval Hospital in the Year 1995

Antibiotic	Number of Treatments	Average Length of Treatment (days)	Reported Cases (only agent involved or combination of ABs[2] excluding clindamycin)	INCIDENCE (%)
Imipenem / Cilastatin	29	4.1	1	3.4
Clindamycin	496	5.9	9	1.8
Other Cephalosporins*	528	6.0	4	0.8
Ciprofloxacin	985	5.8	5	0.5
Ampicillin / Amoxicillin	621	4.3	3	0.5
Amoxicillin / Clavulanate	197	5.4	1	0.5
Cefazolin / Cephalexin	1086	2.7	4	0.4
Cefuroxime	721	4.2	3	0.4
Metronidazole	472	4.1	2	0.4
Other Penicillins**	1459	3.1	5	0.3
Macrolides	402	4.9	1	0.2
Cefaclor	183	5.0	0	0.0
TMP / SMX	396	5.1	0	0.0

* Ceftazidine / Ceftriaxone / Cefoxitin
** Cloxacillin / Penicillin G / Ticarcillin / Piperacillin
1. CDD denotes *C. Difficile* diarrhea
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DISCUSSION

Antibiotic-associated CDD is a significant problem which seems to be on the increase.[1] This is a fact which can be explained by several factors: increased use of broad-spectrum antibiotics, treatment with combination of antibiotics, orally administered antibiotics with a low extent of absorption.[2] Furthermore, it has now been established that CDD can also be a nosocomial disease. The tendency to treat as out-patients those patients moderately infected and to hospitalize those more seriously infected may also explain the progression of the disease, since CDD more

frequently affects severely debilitated hospitalized patients.[1,2] This last point is clearly brought out in our study by the average duration of stay of 17.5 days after the diagnosis of CDD.

CDD is a disease whose social cost cannot be discounted. The high degree of morbidity associated with this condition is demonstrated by the necessity of hospitalizing a third of the patients under study for this condition alone, with an average duration of stay of 5.7 days.

A review of the antibiotic-associated CDD cases carried out at our centre in 1994, and involving 72 patients, had established a link between the use of cefuroxime and the onset of CDD. Cefuroxime was the only antibiotic received by 16 patients (22%) before CDD was diagnosed. If we also consider those cases where the causal link is possible, that is to say when other antibiotics had been used in association with cefuroxime, the incidence rises to 28%. This percentage observed with cefuroxime was even higher than the percentage observed with clindamycin (22%). The results of this review were reported to the pharmacology committee at our centre, but no change was made at that time to the hospital's drug formulary. It has in fact been shown that a restrictive formulary is an efficient method of reducing the number of cases of antibiotic-associated CDD, especially the restriction of clindamycin.[1,9,10,11] This method was not adopted because some doubt had been cast on the validity of the results obtained since these results did not report the incidence as a function of the number of prescriptions made for each of the antibiotics.

The results obtained in the present study demonstrate that 7 cases out of 42 are linked to cefuroxime (17%). If we add those cases where the causal link is possible (association of antibiotics without clindamycin), 10 patients had received cefuroxime before CDD was diagnosed (24%). These results, although lower than those obtained in 1994, still confirm the association between the use of cefuroxime and CDD. On the other hand, since the majority of cases (7) occurred with patients having received a cefuroxime prescription outside the hospital, either as out-patients or in another hospital, the incidence as a function of the number of prescriptions made at Laval Hospital has only been calculated for three patients. The percentage of 0.4% obtained with cefuroxime is one of the lowest calculated. In other studies, contradictory results have been obtained for cefuroxime with regard to the incidence of CDD. In an earlier study carried out in hospitalized patients, a significant risk was associated with the use of 3 antibiotics: ceftazidime, cefuroxime, and clindamycin.[12] Another study published in 1994 had as its main objective to evaluate the etiology of CDD diagnosed by colonoscopy with emphasis on arriving at some understanding of the role played by cefuroxime axetil.[13] This study, which was carried out among ambulatory patients and excluded prescriptions made for hospitalized patients, reports an incidence of 0.7 cases per 100,000 prescriptions for cefuroxime axetil. The lowest incidence calculated is 0.06 / 100,000 for macrolides while the highest is 5.1 / 100,000 for cefixime. The authors conclude that the group of antibiotics made up of cefaclor, cefuroxime axetil, and tetracycline / doxycycline appeared to be rarely or very rarely involved in the etiology of CDD.

With regard to the other antibiotics associated with CDD in our study, it is not surprising to see the higher incidence noted with clindamycin (1.8%) and the other cephalosporins (0.8%). The highest result, obtained for imipenem / cilastatin (3.4%) needs to be interpreted with some caution. The calculated percentage may be biased by the small number of prescriptions (29) made with this agent. The relatively high incidence (0.5%) calculated for ciprofloxacin confirms this antibiotic's strong potential for causing CDD, as recently demonstrated.[12] It must also be noted that another cephalosporin, cefaclor, used in respiratory infections, has not been associated with any case of CDD, either with those who began treatment as out-patients or in hospital. This is confirmation of the very weak etiologic potential of this agent. As demonstrated in other studies,[13,14] this is linked no doubt to highly effective oral absorption thus limiting concentrations in the intestine.[2]

One of the main limitations to studies of CDD in hospitalized patients is the large number of cases reported after the use of several antibiotics administered concomitantly or sequentially. In our study, nearly 80% of the patients with an antibiotic prescription that began at Laval Hospital received antibiotics in association before CDD was diagnosed. Given the high incidence of CDD reported for clindamycin,[2,3] only associations without this agent were used for incidence calculation. Also, we cannot exclude that a hospitalized patient already colonized with the organism can develop the infection with any kind of association of antibiotics. With those treated as out-patients, one antibiotic agent is usually the cause of CDD, but the incidence is difficult to calculate in the absence of data relating to the number of antibiotic prescriptions made for ambulatory patients. It has to be noted that in a retrospective type study it is difficult to establish an exact profile of antibiotic agent consumption among those treated as out-patients. It is thus impossible to exclude totally the use of an antibiotic other than the one mentioned in the patient's chart. There is also a limitation in patient selection by using positive toxin results to select a patient population as false positive and false negative results can occur.

Another limitation is the possibility that some cases of CDD linked to antibiotics prescribed at Laval Hospital

had been diagnosed elsewhere. The incidence reported in this study is therefore probably underestimated.

In conclusion, for those patients who were diagnosed with CDD but whose antibiotic began outside the hospital, cefuroxime was the only antibiotic received in the 2 months preceding the event for half of the patients. For those patients whose treatment began at the hospital, the calculated incidence (0.5%) places this agent in the low-risk category compared with other antibiotics. The agents showing a higher incidence are those usually associated with CDD: clindamycin, third generation cephalosporins, and amoxicillin/ampicillin.[2,6] Cefaclor is not associated with any of the cases of CDD either among ambulatory or hospitalized patients.

CDD is mainly a nosocomial disease which can be prevented in 2 ways: by the adoption of measures designed to control the transmission of infection, and by a more restrictive use of those antibiotics more frequently associated with the disease.[12]

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