Clostridium difficile Colitis Following Antibiotic Prophylaxis for Dental Procedures

(Une colite à *Clostridium difficile* à la suite d'une antibiothérapie prophylactique pour les procédures dentaires)

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Sommaire

La diarrhée et la colite causées par le Clostridium difficile sont des complications courantes de l'antibiothérapie dans le milieu hospitalier. Nous rapportons ici un cas de colite Clostridium difficile suivant une antibiothérapie prophylactique contre l'endocardite, administrée avant les procédures dentaires dans le milieu communautaire. L'infection a nécessité un séjour prolongé à l'hôpital. Les dentistes doivent être conscients de l'importance de la maladie et des risques associés aux antibiotiques, qu'ils servent à la prévention ou au traitement.

Mots clés MeSH : *antibiotics/adverse effects; Clostridium difficile; colitis*

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Clindamycin is enjoying a resurgence in prescribing popularity in community practice. This may be partly owing to its inclusion in the most recent American Heart Association guidelines for the prevention of endocarditis[1] and its attractive antimicrobial spectrum for the treatment of dental infections.[2] Controversy surrounding its role in dental practice has recently been addressed in this journal.[3,4] We present the case of a patient who received antimicrobial prophylaxis for endocarditis prior to dental intervention and who suffered significant morbidity secondary to antibiotic-associated *Clostridium difficile* (*C. difficile*) colitis.

Case

FB is a 71-year-old woman admitted to our tertiary care facility on July 6, 1998, with diarrhea and dehydration. Her past medical history was significant for maturity onset diabetes mellitus, hypertension, cerebrovascular accident with left hemiplegia, ischemic heart disease, congestive heart failure, atrial fibrillation and rheumatic fever at age 19. An echocardiogram performed during a previous hospital admission in early 1998 revealed a left ventricular ejection fraction of 25% and normal mitral and tricuspid valve structures, with trivial to mild regurgitation.

FB reported having a penicillin allergy characterized by hives and difficulty in breathing. Three weeks before admission, she had taken erythromycin and clindamycin as prophylaxis for 2 dental procedures approximately one week apart. The erythromycin was administered as a 1-g dose pre-procedure and a 500-mg dose 6 hours post. The clindamycin was given as a single pre-procedure dose of 600 mg.

FB was alert and oriented on presentation to hospital. She had a temperature of 38.4°C with a respiratory rate of 20 and required a fluid bolus because of orthostatic hypotension. She had been experiencing watery, foul-smelling diarrhea with streaks of blood up to 20 times per day for approximately 10 days. Associated complaints included diffuse abdominal cramping, intermittent nausea and vomiting and inability to eat solid food for the past 5 days. Bowel sounds were normal. The abdomen was mildly distended, soft and diffusely tender. There was voluntary guarding without rebound, masses or organomegaly. Three views of the abdomen revealed gas throughout the bowel but no air fluid levels or dilatation. Her white blood cell count was 16.6 x 10e9 cells/L (neutrophils 14.9). The differential diagnosis was viral disease, *C. difficile* colitis, diabetic diarrhea or diverticulitis.

FB was empirically started on intravenous cefazolin, gentamicin and metronidazole. Blood cultures taken on admission were negative. Stool cultures were negative for ova and parasites, but positive for *C. difficile* toxin. The cefazolin and gentamicin were stopped within 48 hours, and therapy with oral metronidazole 250 mg 4 times a day was administered for a total of 7 days for *C. difficile*. The diarrhea initially improved, but by July 18 the

patient was again having up to 7 liquid bowel movements per day with repeat stool toxin positivity. The gastroenterology service was consulted. Metronidazole was resumed at a dose of 500 mg orally 3 times a day on July 22 and was continued until August 1. The impact of the persistent infection on the patient's blood sugar necessitated intensive management by the endocrinology service. Rehabilitation by physical and occupational therapy was also necessary. Her condition and strength gradually improved, and FB was discharged from hospital on August 31.

Discussion

Antibiotic-associated diarrhea (AAD) and colitis are important and increasingly frequent complications of antibiotic use.[5] Infection with the micro-organism *C. difficile* is responsible for up to 20% of cases of AAD and for virtually all cases of pseudomembranous colitis (PMC).[6] The potential manifestations of *C. difficile* include asymptomatic carriage, diarrhea, PMC, toxic megacolon and colonic perforation.[7] Although medical management is effective in the majority of patients,[6] surgical intervention may be necessary in 5% to 20% of cases.[8,9] Relapse following medical management, as was seen in our patient, occurs in about 20% to 23% of patients.[10]

Symptomatic infection with *C. difficile* has been shown to contribute to increased hospital costs, morbidity and mortality.[11-14] Miller and others[14] examined the health care burden of *C. difficile* diarrhea in 19 Canadian hospitals and found a prevalence of 5.86 per 1,000 admissions. Mortality directly due to *C. difficile* diarrhea was 1.5%. The cost for readmission alone for nosocomial *C. difficile* diarrhea per year was estimated at $128,200 per site.

AAD and colitis occur most often in hospital and nursing home environments rather than in the community setting.[5] McFarland and others[15] found that approximately 5% of patients admitted to a general medical ward had community acquisition of *C. difficile* in the stool and that 21% had acquired *C. difficile* during their hospitalizations. Kofsky and others[11] reported that of 155 hospitalized patients with positive *C. difficile* toxin assays, only 8 patients (5.2%) had an admitting diagnosis of *C. difficile* infection; the remaining 147 patients (94.8%) acquired the infection during the course of their hospitalization. Riley and others[16] reported *C. difficile* isolation rates of 5.5% and 10.7%[17] in patients presenting with diarrhea in community practice. In a retrospective cohort study of members of a health maintenance organization, the incidence rate of *C. difficile* diarrhea was 7.7 cases per 100,000 person-years.[18] Eighty-two per cent of the cases identified were diagnosed and treated exclusively in the ambulatory care setting. The rate of disease resulting in hospitalization was 0.5 to 1.0 per 100,000 person-years.

In their assessment of the epidemiology of clinically recognized community-acquired *C. difficile* diarrhea, Hirschhorn and others[18] found that increased age and exposure to more than one antibiotic within 42 days were associated with an increased risk of *C. difficile* diarrhea. A concurrent illness or other potentially predisposing factor was present in 43% of patients and included chronic antibiotic treatment, inflammatory bowel disease, human immunodeficiency virus infection and malignancy. Elderly patients with underlying diseases, such as FB, are likely to have frequent hospital admissions as well as antimicrobial exposures (for treatment or pre-procedural prophylaxis), placing them at high risk for *C. difficile* disease.

Although treatment courses of antimicrobials are commonly thought of as a risk factor for *C. difficile* disease, cases involving administration of perioperative doses for surgical prophylaxis have been described.[19,20] Our patient had received 2 different antibiotics in a total of 3 doses for endocarditis prophylaxis associated with her dental procedures in the weeks prior to her hospital admission.

Almost every commonly used antibiotic has been implicated in causing *C. difficile* diarrhea.[5,6] While it is impossible to determine which antibiotic (erythromycin, clindamycin or the combination) precipitated our patient's *C. difficile* infection, we suspect that clindamycin played an important role. The frequent association of PMC with clindamycin in the 1970s caused the condition to become known as "clindamycin colitis."[21] The incidence of *C. difficile*–induced colitis as a complication of clindamycin therapy has been reported to range from 2% to 10%.[22-24] A study monitoring the development of diarrhea in clindamycin-treated and ampicillin-treated patients diagnosed PMC in 2% and 0.3% of patients respectively.[24] Golledge and others[25] reported that the relative risk of *C. difficile*–associated diarrhea was 9.1% for clindamycin compared with 4.4% to 5.1% for various extended spectrum cephalosporins.

The amount of clindamycin dispensed in Canadian retail pharmacies has increased by approximately 133% over a 3-year period from 1996 to 1999.[26] Comparative figures for the province of Ontario demonstrate a 115% increase.[26] It is difficult to predict what the potential impact of the increasing use of clindamycin in community practice will be on the burden of *C. difficile* infection. We suspect that its use in dental infections and as prophylaxis for endocarditis prior to dental procedures has contributed to some of the observed increase. The American Heart Association guidelines for endocarditis prophylaxis historically recommended erythromycin for use in penicillin-allergic patients.[27] In the most recent guidelines, erythromycin is no longer recommended for penicillin-allergic individuals, but clindamycin and other alternatives are offered.[1]

Our patient's need for 56 days of hospitalization, consultation by specialty services and intensive physical therapy to return her to community living clearly demonstrates the significant impact of *C. difficile* diarrhea or colitis on health care costs and patient morbidity. Through this report we hope to heighten awareness among dental practitioners to the significance of the disease and to this risk associated with antibiotics, whether they are used for prophylaxis or treatment. Patients should be informed of the potential for diarrhea with antibiotic prescriptions and be instructed to follow up with their family physician should diarrhea occur within 2 months of therapy. Prudent use of narrow spectrum antibiotics, for the shortest possible duration and in only those patients with well-defined indications for prophylaxis or treatment, will minimize the risk of *C. difficile* disease. Avoiding the unnecessary use of antibiotics is the most important step that health care prescribers can take to prevent the morbidity and mortality associated with *C. difficile* disease. ◆

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