**Clostridium difficile** Outbreak: A Small Group of Pharmacists Makes a Big Impact

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**INTRODUCTION**

Hospitals all over Canada are realizing that **Clostridium difficile** can kill. The Royal Victoria Hospital in Barrie, Ontario, declared a **C. difficile** outbreak on February 23, 2007, after 39 new cases of **C. difficile**–associated disease (CDAD) were identified since the start of the year. Before this period, the baseline monthly incidence of hospital-acquired CDAD at this institution had been about 8. A subsequent external chart audit of 31 cases from September 2006 to February 2007 concluded that **C. difficile** had hastened or had been the primary factor in the deaths of 7 patients at the hospital and had been a contributing factor in 11 more deaths. In response to the outbreak, the Royal Victoria Hospital implemented a 50-point action plan, which included increasing infection control measures, such as enhancing cleaning practices, hand hygiene, and isolation precautions; extensive staff and patient education; and intensive review of antibiotic therapy for all patients at high risk of CDAD. The purpose of this paper is to describe how the pharmacy department at the Royal Victoria Hospital responded to the challenge of the outbreak, in particular by developing a program to help reduce the rate of CDAD within the hospital. Despite a reduced complement of pharmacists and minimal clinical presence on the patient care units, the pharmacy department designed and implemented clinical decision support tools, provided education, and promoted antibiotic stewardship to minimize the risk of CDAD. The leadership and clinical expertise of the pharmacy department contributed to a reduction in new cases of nosocomial CDAD at the hospital and raised awareness about the pressing nature of **C. difficile** infection.

**BACKGROUND**

**Clostridium difficile** is a gram-positive, spore-forming anaerobic bacillus that has been an identified cause of nosocomial diarrhea for at least 30 years. Up to 25% of patients experiencing diarrhea associated with antibiotics and 95% of patients with a diagnosis of pseudomembranous colitis test positive for *C. difficile* toxin. CDAD ranges from mild diarrhea to sepsis or even death. There are many risk factors for acquiring **C. difficile**: a history of antibiotic use; invasive procedures of the gastrointestinal tract; prolonged hospital stay; use of other medications, such as chemotherapeutic agents or proton pump inhibitor therapy; debilitation; and older age. The bacterium is transmitted via the oral–fecal route, which makes hand and environmental hygiene the most effective way of containing transmission.

A hypervirulent, fluoroquinolone-resistant strain of **C. difficile**, known as BI/NAP1, has emerged in Canadian hospitals. This new strain is leading to increased morbidity and is making containment more difficult. A Quebec study based on data obtained during an epidemic of the BI/NAP1 strain found that patients with CDAD had a cumulative attributable mortality of 16.7% relative to a control group without CDAD. The Royal Victoria Hospital experienced the virulence of this strain first-hand in 2007.

The Royal Victoria Hospital is a 300-bed community hospital located about 100 km north of Toronto, Ontario. It serves a large geographic area and records more than 80,000 emergency visits per year. In response to an increase in nosocomial cases of **C. difficile** infection at the beginning of 2007, the hospital declared an outbreak and immediately implemented formal measures to reduce the rate of **C. difficile** infection. The hospital worked closely with the local health unit and immediately requested the assistance of an external expert advisory panel of infection control practitioners from the University Health Network in Toronto. The outbreak was officially declared over on July 25, 2007.

Microbiological testing during the outbreak identified the BI/NAP1 pathogen. Not all samples were typed, and not all tested samples were of the BI/NAP1 strain; however, it was recognized that infection control practices had to target the more virulent pathogen. Although infection control practices such as hand hygiene and stringent environmental cleaning...
policies were already in effect, opportunities for improvement were identified. For example, overcrowding within the hospital was thought to be contributing to the outbreak. In the first 2 months of 2007, bed shortages meant that a total of 1400 patients had been cared for temporarily in hallways or overflow units. Other identified shortcomings included a lack of handwashing facilities and inadequate availability of disposable or patient-specific resources such as commodes. By implementing an aggressive action plan, the hospital contained the outbreak more quickly than the expert advisory committee had predicted. Part of that success was due to the effort of a small group of pharmacists working within the pharmacy department.

The Royal Victoria Hospital values the clinical contribution of pharmacists and budgets for about 11 full-time equivalents (FTE) annually. However, during the outbreak period, the pharmacy department was functioning with a maximum of 7 and often only 5 or 6 FTE pharmacists. This staff shortage was due to unanticipated staffing losses, as well as nationwide recruitment difficulties. To provide adequate distributive services, the hospital maximized the responsibilities assigned to technicians, but was still forced to severely reduce clinical representation on patient care teams. Pharmacists were physically present only in the oncology unit and, to a limited extent, the critical care unit. Clinical services were provided from the centralized pharmacy with the assistance of technological tools, as described below.

The Royal Victoria Hospital uses an electronic medical record system from which pharmacists can access laboratory and microbiological results, consult notes, diagnostic imaging results, and information about past admissions, as well as drug information databases. The Ontario Drug Benefit program provides access to a list of prescriptions that have been filled in the community for program beneficiaries. However, daily progress notes and nursing notes are not available from the pharmacy department. With limited clinical presence, a staffing shortage, and incomplete patient information, addressing the C. difficile outbreak presented a challenge to the pharmacy department.

**PROGRAM DESCRIPTION**

Part of the outbreak action plan included review of antimicrobial therapy and a review of antibiotic use within the hospital. To achieve these objectives and to reduce the rate of CDAD within the hospital, the hospital looked to the pharmacy department for clinical direction and leadership. The pharmacy department approached this challenge with the goal of providing therapeutic decision support based on the best evidence available. After reviewing the literature, consulting with experts and colleagues to understand the nature of C. difficile infection, and assessing the available evidence for CDAD treatment and prevention, staff in the pharmacy department developed a 3-pronged approach. The department would promote antibiotic stewardship, design and implement clinical decision-support tools to guide antibiotic therapy, and provide extensive education for pharmacy staff and physicians at the hospital. It was felt that this approach, which was approved by the University Health Network expert advisory panel, would address the main pharmaceutical issues of the outbreak.

**Antibiotic Stewardship**

Infection control, environmental interventions, and antibiotic stewardship are the most important factors to combat CDAD. As most cases of CDAD are associated with exposure to antibiotic, ensuring appropriate antibiotic usage was deemed a suitable starting point. Although controversy exists about the impact of antibiotic agents on C. difficile, it has been established that appropriate antibiotic prescribing can reduce the rates of hospital-acquired infections, including CDAD.

When pharmacists at the hospital reviewed patterns of antibiotic usage, they identified several opportunities for improvement, which were then discussed with physician groups: antibiotic coverage was not consistently tailored on the basis of culture, susceptibility, and clinical response after initiation of broad-spectrum agents; current therapeutic pathways, such as those for community-acquired pneumonia and chronic obstructive pulmonary disease (COPD), appeared to encourage the use of fluoroquinolones, which could theoretically increase the prevalence of the fluoroquinolone-resistant BI/NAP1 strain; and surgical prophylaxis regimens were not always based on available evidence. Positive aspects of antibiotic usage at the Royal Victoria Hospital included strictly enforced automatic stop dates for antibiotics and adherence to formulary restrictions. The University Health Network expert advisory panel and the pharmacists and physicians at the hospital viewed appropriate antibiotic selection and prescribing practices as an integral step in reducing rates of CDAD. To promote antibiotic stewardship, pharmacists met with surgeons, intensivists, emergency physicians, and the hospital’s chief of staff to build consensus about amendments to the various therapeutic pathways and more prudent antibiotic prescribing practices. The guidelines for community-acquired pneumonia and COPD were revised, and these revisions were fast-tracked through the Pharmacy and Therapeutics Committee within a month, but a more immediate response to antibiotic selection was also required. The pharmacy department achieved this by creating several clinical decision support tools, described in the next section.

**Clinical Decision Support Tools**

To specifically address the C. difficile crisis, the pharmacy department developed an algorithm for antibiotic surveillance
by pharmacists (Figure 1). The pharmacists used this algorithm in the central dispensary when assessing antibiotic orders for both patient-related and drug-related CDAD risk factors. Based on extrapolations from the published literature and consultation with the University Health Network expert advisory panel, antibiotics were classified as having high, intermediate, lower, or lowest CDAD risk. Although the impact of individual antibiotics on C. difficile is controversial and the ranking of CDAD risk for these agents was extrapolated from the literature, this approach was deemed appropriate by

**Figure 1.** Algorithm for antibiotic surveillance by pharmacists at the Royal Victoria Hospital, Barrie, Ontario. CCU = clinical care unit, CDAD = Clostridium difficile–associated disease, EMR = electronic medical record, GI = gastrointestinal, micro = microbiology, MRP = most responsible physician, NG = nasogastric.
the University Health Network expert panel. Patient-related 
CDAD risk factors of greatest concern were age over 65, severe 
comorbidity, recent gastrointestinal intervention (including 
nasogastric intubation), and duration and frequency of 
hospital admission. All of this information was generally 
accessible through the electronic chart. Pharmacists followed 
the algorithm to identify antibiotic orders that might be 
putting patients at greater risk of CDAD. The objective of this 
risk assessment was to select appropriate antibiotics from the 
lowest possible risk category for the patients who were most 
vulnerable to CDAD, while still conforming to best practice. 
Professional judgement was exercised during this process, and 
diligent monitoring was implemented if patients were changed 
to more nephrotoxic therapies. Avoiding the antibiotics with 
the highest CDAD risk was not always clinically appropriate. 
If the algorithm indicated an opportunity for therapeutic 
modifications, the pharmacists communicated the recommenda-
tions directly to the most responsible physician and docu-
mented the change in the patient's electronic medical record.

The microbiology department faxed a daily report of the 
hospital's culture and susceptibility results to the pharmacy 
department. This direct collaboration allowed pharmacists to 
monitor the microbiological efficacy of therapeutic inter-
tentions. Monitoring of clinical efficacy was left to the discretion 
of the patient care team. The patient care team was also critical 
in identifying patients who were experiencing diarrhea that 
might have been related to \textit{C. difficile} infection.

A program to help end the \textit{C. difficile} outbreak also needed 
to include early and appropriate treatment of symptomatic 
CDAD. To facilitate prompt therapeutic intervention, the 
pharmacy department contributed to the creation of a preprinted 
physician order form for \textit{C. difficile}–associated diarrhea. The 
order sheet included treatment options and preferred length of 
therapy, encouraged the discontinuation of current antibiotics 
if possible, and specified that any antidiarrheal agents should be 
discontinued. The order form also specified a mandatory 
pharmacist consult within 72 h. The consult gave pharmacists 
another opportunity to review all of the patient's drug therapy, 
such as antibiotics, laxatives, antiperistaltic agents, and opiates, 
as well as providing a method to track patients who were 
receiving CDAD therapy. Once a patient had been started on 
CDAD therapy, the infection control practitioners worked with 
the patient care teams to monitor therapeutic response. 
Pharmacists continued to provide guidance and clinical 
expertise by establishing open lines of communication with the 
patient care team. Communication and collaboration were also 
developed through education of physicians.

\textbf{Education}

Education was considered an important element of the 
hospital's and the pharmacy department's action plans. All 
hospital staff were strongly encouraged to undertake education 
about \textit{C. difficile}. Such education was provided through a 
collaborative approach with education services at the hospital, 
in the form of in-service sessions, bulletins, and other teaching 
modalities. In addition, the pharmacy department ensured 
that pharmacists were kept up to date on CDAD risk factors, 
\textit{C. difficile} transmission, and therapeutic options through 
presentations, written communication, and learning opportu-
nities with guest experts on CDAD. The pharmacy department 
offered education about drug therapy and antibiotic steward-
ship to physicians through meetings with physician groups, 
written newsletters, and verbal communications.

Pharmacy technicians were also educated to ensure 
compliance with environmental procedures (especially with 
respect to designated medication carts) and order-entry 
procedures (given that the duration of therapy for CDAD 
treatment was longer than the routine automatic stop time for 
other antibiotics). Professional learning helped to raise aware-
ness about \textit{C. difficile}, improved intergroup collaboration, and 
increased practitioner confidence. Education, promotion of 
antibiotic stewardship, and provision of clinical decision 
support tools all contributed to reducing the rate of CDAD at 
the Royal Victoria Hospital.

\textbf{PROGRAM RESULTS}

The clinical decision support tools were designed and 
implemented within the first 2 weeks of the hospital declaring 
the \textit{C. difficile} outbreak. Although there is no way to measure 
the direct impact of the pharmacy department's program on the 
rate of CDAD, the rate of identification of new nosocomial 
cases dropped by mid-March 2007 (Figure 2). In fact, the 
identification of new cases actually dipped in February, before 
the official declaration of an outbreak, possibly because staff 
had already commenced more diligent infection control 
practices and surveillance in response to a general sense among 
pharmacy staff that an unusually high number of cases of 
CDAD were being identified. Pharmacists were already 
monitoring antibiotic therapy and recommending therapeutic 
alternatives as part of routine clinical monitoring, although not 
consistently. These efforts may have contributed to reducing 
CDAD cases before implementation of the hospital action plan 
and other initiatives. By the end of July, the outbreak was 
officially over, and the pharmacy department was able to reflect 
upon the limitations and challenges of the program.

The biggest challenge faced by the Royal Victoria 
Hospital pharmacy department during the \textit{C. difficile} outbreak 
was designing a useful program that could be implemented 
effectively from the central pharmacy without greatly increasing 
workload. The antibiotic surveillance algorithm was easily 
integrated into the existing order screening process and, once 
pharmacists became familiar with it, the impact on workload

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was minimal. Even after the outbreak was over, the pharmacists continued to use the algorithm to identify patients at risk of CDAD.

Another challenge was getting physician groups together for education and to develop consensus on guidelines. Not all physician groups appreciated the urgency of the situation or the potential risk that C. difficile presented to their patients. However, as hospital-wide education progressed, this resistance declined. Earlier implementation of education and stronger collaboration with internal infectious disease specialists from the outset of the outbreak might have facilitated dissemination and acceptance of proposed changes to practice.

Measuring the success of a program is always important. However, because of the immediacy and urgency of the outbreak, evaluation strategies were not included as part of the program. Therefore, the true benefit of the pharmacy department’s initiatives could not be measured. Program evaluation should be part of future endeavours of this kind.

**FUTURE DIRECTIONS**

As with any reactive program, the work of the Royal Victoria Hospital pharmacy department during the CDAD outbreak left room for improvement. Future revisions to the clinical decision support tools must incorporate new evidence as it becomes available. The decision to approach antibiotic selection on the basis of CDAD risk levels was supported by the University Health Network expert advisory panel. However, any future evidence supporting a different approach would need to be considered. Automatic stop dates for antibiotics are established and enforced within the Royal Victoria Hospital, but opportunities may exist to further influence the duration of therapy for conditions such as urinary tract infection and community-acquired pneumonia. Duration of exposure to antibiotics may become more important than restricting any single agent or class.

Antibiotic stewardship must become a continuing process, with more emphasis on routinely updating treatment guidelines and building upon the collaborative success achieved during the C. difficile outbreak. Future guideline revisions should address the requirements for and the selection and duration of postoperative antibiotic therapy. Good antibiotic stewardship also requires appropriate tools such as pocket references and antibiotic information programs for hand-held devices. Ensuring that medical staff have ready access to antibiotic references may be an area to explore.

The role of proton pump inhibitors in CDAD was not addressed through the CDAD control program at the Royal Victoria Hospital. Evidence now suggests that these agents may be independent risk factors for CDAD.\(^1\)\(^2\)\(^3\) As more evidence emerges, the pharmacy department will need to consider this issue and incorporate recommendations on the use of these drugs. Proton pump inhibitor therapy may also be associated with an increased risk of CDAD recurrence.\(^9\) General guidelines on the appropriate management of CDAD recurrence or relapse would be beneficial and should include the potential discontinuation of proton-pump inhibitors, the benefit of tapering CDAD therapy, and pulse therapy with antimicrobial agents. Providing education and guidance on this issue could be a future direction for the pharmacy department.

Another potential future consideration is the role of adjunctive agents such as cholestyramine and probiotics in the prevention and treatment of CDAD. In 2007, there was no consensus on the role of probiotics for treating CDAD, and the Royal Victoria Hospital made Saccharomyces boulardii available to patients at the discretion of clinicians. Given the recent work of Pillai and Nelson,\(^10\) who found no conclusive benefit of probiotics as adjuncts to CDAD therapy, this practice may require amendment. Further evidence is needed before conclusive recommendations can be made.

**CONCLUSIONS**

The Royal Victoria Hospital in Barrie, Ontario, implemented a comprehensive action plan when an outbreak of C. difficile occurred in the hospital in February 2007. The pharmacy department developed a program to help reduce the rate of nosocomial CDAD and to provide appropriate treatment. By promoting antibiotic stewardship, designing and implementing clinical decision support tools, and providing...
education, the pharmacy department contributed to rapidly ending the outbreak. Future considerations for the program include incorporating new evidence on CDAD prevention as it becomes available, guiding the therapy of CDAD recurrence and relapse, and assessing the evidence for adjunct agents in the management of CDAD. Even with a reduced number of pharmacists and minimal clinical presence on patient care units, pharmacists were able to give patients at the Royal Victoria Hospital exceptional care and to provide clinical expertise and leadership to other members of the hospital’s staff. A small group of pharmacists at this institution was able to have a big impact on the C. difficile outbreak.

References

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