Clostridium difficile infection in hospitals: risk factors and responses

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An outbreak of a particularly virulent form of *Clostridium difficile*-associated diarrhea (CDAD) and enterocolitis is affecting multiple hospitals in Montréal, resulting in higher-than-expected numbers of intensive care unit admissions, colectomies and deaths. In this issue, Dial and colleagues[1] (see page 33) report on an association between the use of proton pump inhibitors (PPIs) and a greater likelihood of acquiring CDAD. In a cohort of 1187 patients on the medical and surgical wards of one hospital, 9.3% of 591 patients receiving PPIs developed CDAD, compared with 4.4% of 596 patients not receiving PPIs (adjusted odds ratio 2.1, 95% confidence interval 1.2–3.5). At another hospital, in a tightly matched case–control study of 94 patients in each group, PPIs similarly were shown to be an independent risk factor for CDAD.

The intuitively obvious explanation for the increased risk of acquiring this common nosocomial pathogen is that the reduction of gastric acidity abrogates a major host defence barrier against intestinal pathogens. As such, a larger proportion of organisms in the vegetative state and acid-resistant spores ever present in the hospital environment could access the lower gastrointesinal tract. Pathogenesis might not be simply a numbers game, however, and other explanations should be sought. Could PPIs have an independent effect within the colon? Whereas most clinicians regard the effect of PPIs as being localized to the gastric mucosa, studies have confirmed that H^+,K^+-ATPases, the target of PPIs, are present in the colonic mucosa.[2] The function of these pumps and their interaction with the PPI class of compounds remains unclear. In several studies, these membrane proteins appear functionally and biochemically distinct from the gastric proton pump,[3,4] suggesting that the PPI class of drug may not affect their function. However, there are also data that one PPI (lansoprazole) may bind to the colonic mucosa.[5] Whether PPIs affect the function of the colonic protein and subsequently alter the intra-colonic biology of *C. difficile* infection and the production of *C. difficile* cytotoxins A and B in animals or in man is completely unknown. Although PPIs appear to increase the likelihood of CDAD, it would be premature to link severity of infection to the use of PPIs. Infection with particular strains of *C. difficile* capable of expressing more toxin(s), or other undefined virulence characteristics should be considered.

An earlier study showed this association.[6] In light of the evidence, hospitals should review the use of PPIs from a risk–benefit perspective. The Canadian Nosocomial Infection Surveillance Program conducted a detailed study in 19 health care facilities in 5 provinces, observing an attributed mortality rate of 1.5%.[7] Faced with potential serious adverse outcomes, guidelines restricting the current broad use of PPIs should be established. Dial and colleagues' report has triggered a review of this association in Calgary Health Region hospitals in light of a recent resurgence in the number of cases. The use of PPIs has doubled in the past 2 years. This study will also raise patients' concerns within the community. However, in a home setting it is expected that the risk of CDAD will be much lower.[8]

Nevertheless, the PPI story should not be the sole focus. The root cause of outbreaks of *C. difficile* diarrhea in our hospitals relates to the difficulty of practising and maintaining good infection control measures in hospitals. Prevention of transmission of infection in hospitals where there is high occupancy, intensive antibiotic pressure and increasingly complex care of patients in an environment conducive to transmission is a daunting task faced by all front-line health care workers. Many of our hospitals were built long before methicillin-resistant staphylococci (MRSA), vancomycin-resistant enterococci (VRE), extended spectrum beta-lactamase-producing (ESBL) *E. coli* and *Klebsiella* species and multi-drug resistant carbapenemase-producing *Pseudomonas* became commonplace.

Although those of us who work as infection control physicians feel that all Canadians should, when in hospital, have a single room with their own toilet facilities, the reality is that shared rooms in various ratios are often the rule. In Calgary, VRE spread between renal patients housed within an older ward with fewer bathroom facilities. Because of difficulties with renovation, these patients were moved to a newer ward with better patient-to-bathroom ratios for the past few years, and the problem was brought under control. Our bone marrow transplant patients have private rooms, and despite intensive antibiotic pressure, *C. difficile* diarrhea is uncommon in this patient population. Recognizing the need to upgrade our facilities, the Calgary Health Region supported the renovation of one of our wards as the main medical teaching unit such that each patient has his or her own toilet.

Older physical plants in need of renovation also have fewer handwashing facilities. Investigators in the United Kingdom[9] showed that merely examining a patient with *C. difficile* resulted in the detection of the organism on the

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hands of health care workers 28% of the time, and that washing with running water and soap resulted in negative hand culture results. In hospitals with inadequate numbers of sinks, alcohol gel hand rubs have been popularized as a method of hand hygiene, even though we know that *C. difficile* spores are not killed by alcohol. In fact, treatment of stool with absolute alcohol is used to kill other microbes, permitting the easy recovery of *C. difficile* in the laboratory. Therefore, sinks placed at strategic locations to facilitate good handwashing practices are requisites in modern health care facilities. We need our health departments (and politicians) to consider, as opportunities arise to renew our physical plants, to renew them such that they are *naturally* resistant to the transmission of nosocomial pathogens. The physical dynamics of providing care in such settings should reduce the numbers of nosocomial transmissions, reduce health care worker stress and, most important, avert the morbidity and costs of nosocomial infection.

Finally, a word on antibiotics inducing *C. difficile* diarrhea. With the exception of MRSA, these nosocomial pathogens, along with *C. difficile*, are microbes that multiply in the intestinal tract under selective antibiotic pressure. Contamination of the hospital environment with a myriad of gut-amplified nosocomial pathogens is an inevitable consequence of the use of antimicrobials. It is to the risk of patients that virtually all antimicrobials used in hospital or in the community can be selectors for this organism, with the exception of the aminoglycosides. Over the last decade we have observed a reduction in the use of aminoglycosides because of their potential for oto- and nephrotoxicity. Clindamycin, cephalosporins as a class (with particular emphasis on second-and third-generation agents) and ampicillin are regarded as the most common inducers.[10,11] Quinolones have also come into question.[12] Many hospitals have taken steps to reduce or eliminate the use of clindamycin in the face of rising numbers of cases of CDAC[13] and to curb the excessive use of second-and third-generation cephalosporins. Beta-lactam/beta-lactamase inhibitor combinations are generally regarded as less conducive to CDAD induction.[14] Nevertheless, these agents can impair the intestinal flora, with subsequent superinfection. Since the main defence against the proliferation of *C. difficile* is the normal intestinal flora comprised largely of anaerobes, and because it has been shown that the *Bacteroides* species are one of the main missing components of the normal flora in cases of relapsing CDAD,[15] it is also important to restrict the wholesale use of metronidazole where anaerobic coverage is not clinically indicated.[16] Finally, it is paradoxical that the main treatment modality for CDAD is the use of antimicrobial agents, which are themselves likely to suppress the normal intestinal microflora. Recent clinical investigation of the effect of a binding polymer that neutralizes toxins A and B in the colon have shown promise in the non-antibiotic treatment of CDAD.[17–19] It is clear that the prevention and treatment of CDAD need to be optimized both in the hospital and in the community and that multiple solutions are required.

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