

***Clostridium difficile*-associated diarrhea (CDAD) and proton pump inhibitor therapy: CAG Position Statement**



En français voir page xxx

Canadian Association of Gastroenterology, Clinical Affairs

In light of the recent data and an advisory from Health Canada (<http://www.phac-aspc.gc.ca/c-difficile/index.html>), the Canadian Association of Gastroenterology (CAG) has prepared the following position statement on the role of proton pump inhibitors (PPIs) in *Clostridium difficile* infection which we hope will be of use to members, other health care professionals and patients across the country.

PPIs are safe and effective medications

PPIs are among the most widely prescribed medications worldwide (1) and have been used for over 15 years with an excellent safety profile (2-7). They comprise the drug class of choice for managing patients with complicated gastroesophageal reflux disease (GERD) (8) as well as uncomplicated GERD (9) and many other chronic acid-related conditions. In these conditions PPI use is associated with improvements in endoscopic outcome, symptoms, quality of life (for indications that include initial therapy, maintenance treatment and prophylactic use) (2-6,8-16). Furthermore, they have been found to improve patient outcomes in acute upper gastrointestinal hemorrhage (17), and more specifically, in those patients with bleeding peptic ulcers (18).

Only evidence-based and appropriate utilization of PPIs should be encouraged, and this will lead to their cost-effective use

Recent data suggest that overutilization of PPIs is common, especially in their intravenous form in the hospital setting (19-22). Although this class of medications appears to be both cheaper and more effective than alternatives in the management of high-risk patients with bleeding ulcers (23-29), such cost-effective utilization is only realised if PPIs are used for appropriate indications.

Recent exploratory data suggest a possible association between the use of PPIs and *C difficile* infection in a selected subgroup of hospitalized patients

The widely accepted risk factors for the development of *C difficile* infection include exposure to antibiotics (the most common), especially those with a broad-spectrum activity (30); increasing age or illness severity (31-33); hospitalization (34) or residence in a long-term care facility (35); increasing duration of hospital stay (36); and exposure to chemotherapeutic or immunosuppressive agents (37). Additional possible risk factors have included gastrointestinal surgery and the use of nasogastric tubes, stool softeners, gastrointestinal stimulants, antiperistaltic drugs, antacids and enemas (31-33). A recent publication has reviewed this topic (38).

Although limited data to date have shown that decreased gastric acidity leads to prolonged *C difficile* organism or toxin survival (39) or to other infectious diarrheal illnesses (40), a very recent report (41) suggests that PPI utilization is associated with community-acquired pneumonia. *C difficile* infection has also been linked to H₂-receptor antagonist use in an American period prevalence survey (35), and to PPI use in an American case-control study (42).

A recent *C difficile* outbreak in Quebec (43) has facilitated additional research on the topic. A report that included both a cohort study and a case-control study (44) has suggested that a strong association may exist between the use of PPIs and the occurrence of *C difficile* infection (odds ratio approximately 2.5). Unfortunately, these studies have been retrospective, and based on limited data that did not take into consideration a number of important variables relating to hygiene practices. Also, the analyses may not have adequately accounted for other known confounding variables. Nonetheless, these results point to a possible causal association between PPI use and the

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development of *C difficile* infection, at least in a specific patient population, and warrant further research. It is important to note that the population found to be at risk in the most recent studies was comprised of older (mean age 73 to 76 years), particularly sick in-patients (14% renal failure, 22% diabetes and 25% cancer), who were also prescribed antibiotics. In fact, in only one of 94 cases did the patient develop *C difficile* infection on a PPI while off antibiotics. Currently, there exist no published data establishing an association between PPI use and *C difficile* infection in an out-patient setting.

The generalizability of the situation currently experienced in Quebec remains in question not only vis-à-vis the type of patients affected, but also with regard to the actual bacterial strain involved. Indeed, in the Quebec outbreak, as for those noted in five American states, it would appear that a special "binary toxin positive" strain (in addition to the production of toxins A and B) has been implicated as the dominant clone (Louie T, personal communication). But only about 5% of all *C difficile* strains produce such a binary toxin, which may be responsible for increased pathogenicity. The situation in Quebec, and results generated from the outbreak, may thus also be region-specific. Quinolone resistance has been raised as a possible additional issue.

The risks and benefits of administering or discontinuing a PPI for a given patient needs to be carefully assessed on a case-by-case basis

Because of the proven benefits of PPI administration in patients with appropriate indications, a decision not to initiate PPI treatment needs to be taken after carefully weighing the risks and benefits for that particular patient. The highly selected nature of the patient population that appears to be at added risk for *C difficile*-associated diarrhea disease with PPI usage, again needs to be emphasized. The CAG wishes to remind health professionals of the importance of appropriate antibiotic prescribing and sound hygiene practices as recognized components to controlling *C difficile*-related illness (38,45,46).

The CAG encourages its members, and indeed all health professionals, to keep abreast of any additional publications of relevant data

It is very likely that clinically relevant animal and human data will soon emerge to further characterize a possible association between the use of PPIs and *C difficile* in various clinical settings. Health professionals are strongly advised to keep abreast of this evolving area of research, and the CAG will endeavor to disseminate up-to-date information and provide guidance in the form of position statements such as this one, or in the form of more extensively developed consensus guidelines, if and when appropriate.

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