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Inpatient Proton Pump Inhibitor Administration and Hospital-Acquired *Clostridium difficile* Infection: Evidence and Possible Mechanism

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ABSTRACT

The incidence of *Clostridium difficile* infection continues to increase globally. Particularly concerning are hospital-acquired cases that attribute significant morbidity, mortality, and expenditures to the health care system. Proton pump inhibitors, which are widely prescribed and generally considered to have minimal adverse effects, have recently come under scrutiny for positive associations with *C. difficile* infection development. This article will specifically review the current state of evidence demonstrating a positive association between nosocomial proton pump inhibitor administration and the incidence of hospital-acquired *C. difficile* infection. In addition, the article delivers state-of-the-art knowledge relative to mechanisms by which proton pump inhibitor exposure may propagate the manifestation of *C. difficile* infection.

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INTRODUCTION

Clostridium difficile infection has become one of the most common health care-associated infection in the US. The morbidity, mortality, and medical care of *C. difficile* infections cost acute care facilities over $6.3 billion yearly.[1] Each incidence of hospital-acquired *C. difficile* infection is associated with an excess cost of up to $29,000[2] and a 9.3% mortality rate.[3] The Centers for Disease Control and Prevention has categorized *C. difficile* infection as an urgent threat to public health, necessitating more monitoring and preventative strategies.[4]

Antibiotic administration, particularly broad-spectrum antibiotics, is the most well-known causal factor for *C. difficile* infection development. Recently, proton pump inhibitor (PPI) administration has garnered considerable attention for its potential role in promoting *C. difficile* infection. This is concerning, as PPIs are among the most commonly prescribed medications globally, 20%-82% of which lack an indication.[5] Approximately 50% of the nosocomial population is prescribed a PPI driven by new and preexisting indications of dyspepsia and prophylaxis of gastrointestinal bleeding or stress ulcer prevention.[6]

In this article we aim to review the current status of medical literature regarding the role of nosocomial administration of PPIs and their role in the development of hospital-acquired *C. difficile* infection.

PROTON PUMP INHIBITOR INITIATION DURING HOSPITALIZATION

Over a 5-year surveillance period, PPI use increased substantially at a large, urban medical center with a concomitant

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decrease in histamine-2 receptor antagonist (H2RA) use over the same time period.[7] The annual incidence of hospital-acquired *C. difficile* infection increased significantly from 5.08 to 8.42 cases/1000 admissions during the same 5-year study period ($P = .0005$). The authors observed a perfect correlation between the increase in PPI use and the increase in hospital-acquired *C. difficile* infection incidence ($r_s = 1.0$; $P = .017$), a result reflective of patterns observed on a national level with coinciding upward trend in PPI prescriptions and *C. difficile* infection incidence.

The investigators also performed a case-control study to examine the impact of PPI on hospital-acquired *C. difficile* infection development controlling for antibiotic use. Patients receiving PPIs prior to or during admission were found to be significantly associated with hospital-acquired *C. difficile* infection (odds ratio [OR] 2.61; $P = .0001$). Moreover, a subanalysis of PPI-naïve patients revealed that first-time use of a PPI occurring during hospital stay remained significantly associated with hospital-acquired *C. difficile* infection (OR 2.57; $P = .0016$). This study reveals several concerns related to nosocomial administration of PPI. First, as overall PPI use increases, so do hospital-acquired *C. difficile* infection cases. Second, continuation of an outpatient PPI during hospitalization is associated with hospital-acquired *C. difficile* infection. Finally, newly initiated PPI increased risk of developing hospital-acquired *C. difficile* infection during hospitalization.

Barletta et al identified a duration threshold as short as 1-2 days at which PPI administration increases *C. difficile* infection risk.[8] A total of 201 patients were evaluated, 67 cases of hospital-acquired *C. difficile* infection and 134 matched controls. PPI had been received by 64/201 (32%) patients in the 30 days prior to hospitalization. Upon hospitalization, the number receiving a PPI increased by nearly 40%, representing new PPI therapy, to 103/201 (51%). Patients developing hospital-acquired *C. difficile* infection were more likely to have received a PPI prior to hospitalization (52% vs 22%; $P < .001$) and during hospitalization (76% vs 39%; $P < .001$). As the duration of PPI use increased, the risk for hospital-acquired *C. difficile* infection also increased, adjusted for length of hospitalization ($P = .018$). A duration of use threshold at which risk of hospital-acquired *C. difficile* infection increased occurred with as little as 1 day of PPI in patients with a previous hospitalization, and 2 days of PPI in previously un-hospitalized patients ($P < .001$). The findings suggest that PPIs for short courses of 1-2 days while hospitalized, as seen when used for stress ulcer prophylaxis (SUP), can place patients at an increased risk of developing hospital-acquired *C. difficile* infection.

CLINICAL SIGNIFICANCE

- Proton pump inhibitors (PPI) enhance hospital-acquired *Clostridium difficile* infection (HACDI)
- Short course PPIs of 1-2 days heighten risk for HACDI
- PPIs combined with antibiotic therapy synergistically enhance risk for HACDI
- PPIs may improve *C. difficile* spore survival and toxin expression
- PPIs may negatively affect neutrophilic host defense mechanisms

Patients admitted to the intensive care unit (ICU) are considered to be at high risk for stress ulcer development, and pharmacologic gastric acid suppression is routinely ordered as SUP. A retrospective study evaluated 3286 critically ill patients during their ICU stay.[9] Most received SUP (91.3%), and PPI therapy was the most common SUP modality (72.6%). During the course of ICU management, 3.3% of patients developed hospital-acquired *C. difficile* infection. The development of hospital-acquired *C. difficile* infection was associated with a longer ICU stay and increased ICU death (OR 1.59). Receipt of a PPI was identified as a substantial contributor to developing hospital-acquired *C. difficile* infection in the ICU by multivariate analysis (OR 3.11). H2RAs were not observed to increase the risk of hospital-acquired *C. difficile* infection.

In an effort to understand the effect that increasing acid suppression might have on risk for hospital-acquired *C. difficile* infection, over 100,000 admissions were reviewed at a large, urban medical center.[10] Admissions were divided into 4 groups (no acid suppression, H2RA, daily PPI, and more than daily PPI) and assessed for incidence of hospital-acquired *C. difficile* infection. After adjusting for other known risks, investigators observed that as the level of acid suppression increased, the odds of developing hospital-acquired *C. difficile* infection both clinically and statistically increased from OR 1.53 for H2RA, to 1.74 for daily PPI, and to 2.36 for more than daily PPI. Compared with no acid suppression, daily PPI increased the risk >70% and more than daily PPI doubled the risk for hospital-acquired *C. difficile* infection.

These studies provide supportive evidence that new initiation of PPI therapy in the hospital, even for short courses of 1-2 days, heightens risk for hospital-acquired *C. difficile* infection. The risk is present not only when compared with no acid suppression, but also when compared with H2RA therapy.

CONTINUATION OF OUTPATIENT PROTON PUMP INHIBITOR PRESCRIPTION DURING HOSPITALIZATION

As one of the most widely prescribed medications in the US, many patients are already established on PPI therapy prior to hospitalization. Upon hospitalization, PPI therapy is continued, also posing a risk for hospital-acquired *C. difficile* infection.

Dial and colleagues reviewed 81 hospitalized patients diagnosed with hospital-acquired *C. difficile* infection in a cohort study.[11] PPI exposure was the primary variable of interest,