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## Inappropriate Antibiotic Use and Gastric Acid Suppression Preceding *Clostridium difficile* Infection

*To the Editor*—*Clostridium difficile* infection (CDI) is a major cause of healthcare-associated diarrhea and the most common cause of healthcare-associated infections (HAIs) in the United States, representing 12% of all HAIs each year.<sup>1</sup> CDI has been labeled an “urgent” threat to public health by the Centers for Disease Control and Prevention (CDC).<sup>2</sup> The major established risk factor for CDI is antibiotic use.<sup>3</sup> Currently, 60% of inpatients receive antimicrobials,<sup>4</sup> and up to 73% of CDIs are preceded by inappropriate antimicrobial use.<sup>5</sup> Other risk factors for CDI have been identified, notably gastric acid suppression medications, which have been associated with an increase in CDI.<sup>3,6</sup> To our knowledge, no

studies have investigated the frequency of inappropriate gastric acid suppressant medication use preceding CDI.

To understand how often CDI is related to inappropriate medication use, we evaluated appropriateness of antimicrobial therapy and gastric acid suppression preceding CDI acquired in an integrated healthcare system. We conducted the study within the Veterans’ Affairs (VA) Maryland Health Care System, which has a total of 727 inpatient beds, including an acute-care medical center, 2 long-term care community living centers, and outpatient clinics. The study was approved by the University of Maryland School of Medicine Institutional Review Board and the Baltimore VA Research and Development Board. Eligible patients were 18 years of age and older with a primary, recurrent, or reinfection case of CDI that occurred between October 2013 and December 2014. Patients were identified from a list of all *C. difficile* toxin gene polymerase chain reaction (PCR)-positive assays during this period. Medical records of PCR-positive patients were reviewed by 1 of 2 physicians (J.L. or M.D.) for confirmation of CDI diagnosis. Type of CDI was classified according to CDC definitions and Society for Healthcare Epidemiology of America (SHEA)-Infectious Diseases Society of America (IDSA) joint practice guidelines.<sup>3,7</sup> Primary CDI included new onset symptoms and PCR-positive toxin assay. Recurrent CDI had recurrent symptoms and positive test within 8 weeks of resolved primary CDI, while reinfection cases occurred >8 weeks after the positive CDI test.

Gastric acid suppressant medications prescribed in acute care, long-term care, or primary care settings within 8 weeks preceding CDI diagnosis were reviewed and assessed for appropriateness of diagnosis, start, and maintenance of gastric acid suppression therapy using AGA guidelines.<sup>8</sup> Appropriate indications for gastric acid suppression were gastroesophageal reflux disease (GERD), acute upper gastrointestinal bleed, peptic ulcer disease, and intensive care unit (ICU) stress ulcer prophylaxis.

All antibiotics prescribed up to 8 weeks prior to CDI diagnosis were also reviewed. Appropriateness of diagnosis of infection, antibiotic spectrum, and treatment duration were determined as in past studies, using SHEA-IDSA guidelines.<sup>3,9,10</sup>

During the study period, 50 patients and 71 episodes of CDI occurred. Forty-nine patients were male and 12 patients were readmitted following the first episode. The average patient age was 66.8 years (standard deviation [SD], 12.3; range, 39–94 years) and median length of stay for acute care patients was 20.2 days (interquartile range, 1–28.5 days). Most episodes were primary infections (60.6%; Table 1). Of all 71 episodes, 63.4% received inappropriate antibiotics prior to infection. Among the 62 episodes treated with antibiotics prior, 45 (72.6%) were inappropriately treated, most commonly due to use of antibiotics without any evidence of infection (59.6% of antibiotic courses) and overly long courses (25% of antibiotic courses). In addition, inappropriate antibiotic use continued after diagnosis of CDI in 38% (27 of 71) of all episodes. In the subset of CDI patients remaining on antibiotics, inappropriate use occurred in 27 of 42 (64.3%) of episodes.

Of all CDI episodes, 38.0% (27 of 71) were preceded by inappropriate gastric acid suppressant medications. For the 40 episodes in which gastric acid suppressant medications were used prior to CDI, 27 (67.5%) were inappropriately treated. The most common causes of inappropriate gastric acid suppression<sup>8</sup> were prolonged treatment of GERD without recurrent symptoms or risk, peptic ulcer disease beyond 1 year, or inappropriate stress ulcer prophylaxis.

Pneumonia, sepsis, skin and soft-tissue infections, and urinary tract infections were all common indications for antibiotics therapy. Inappropriate courses of antibiotics were most commonly initiated in long-term care (88.9% of courses inappropriate), outpatient clinics (72.7% inappropriate), and the emergency department (71.4% inappropriate).

We found that CDI was often preceded by inappropriate antibiotics and inappropriate gastric acid suppressant medication. Prior CDI antibiotic use was often inappropriate due to absence of any evidence of infection or courses too long in duration. Once diagnosed with CDI, patients continued to receive inappropriate antibiotics. Antibiotics were more often inappropriate when started outside of acute care. Inappropriate gastric acid suppressant medication preceded more than a third of all CDI episodes.

This study included a modest number of episodes of CDI. However, we included data regarding all CDI episodes for more than a year<sup>7</sup> within an integrated healthcare system, which also permitted more complete knowledge of antibiotic use prior to CDI diagnosis than studies focused solely in the acute care setting.<sup>5</sup> Additionally, our study is one of the first to examine frequency of inappropriate gastric acid suppression medications prior to CDI diagnosis and the frequency of continued inappropriate antibiotic use following CDI diagnosis.

Despite hospitals increasing stewardship efforts, our results suggest that inappropriately prescribed antibiotics are still common before and after CDI diagnosis. Continued focus on reducing inappropriate antibiotic use and increased efforts to reduce inappropriate gastric acid suppressant use, both established risk factors for CDI, may represent an opportunity to decrease CDI. Emphasizing concrete patient-level risk of CDI may improve appropriate use of antibiotics and gastric acid suppressant medications.

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