Clostridium Difficile Infection

Prevention, Treatment, and Surgical Management

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KEYWORDS

• Vancomycin • Fecal microbiota therapy • Ileostomy • Colectomy

KEY POINTS

- Infection control measures and strategies, including isolation and personal barrier precautions, handwashing, bleach-based environmental cleaning, and antibiotic stewardship, are paramount to prevent *Clostridium difficile* infection.
- Severity scoring and stratification of disease severity is necessary to ensure appropriate therapeutic management.
- Early recognition of patients with complicated disease, with early surgical consultation, improves outcomes.
- Surgical therapies should be considered early in the setting of clinical deterioration.
- Loop ileostomy and colonic lavage should be considered as an alternative to subtotal colectomy in the absence of colonic perforation, necrosis, or abdominal compartment syndrome.

INTRODUCTION

Antibiotic-associated colitis was initially reported in the 1970s after the introduction of clindamycin, and at that time was referred to as clindamycin-associated colitis. Tedesco and colleagues[1] reported endoscopy findings on 200 patients who received clindamycin and showed a 20% incidence of diarrhea and a 10% incidence of pseudomembranous colitis. *Clostridium difficile* as the causative agent of antibiotic-associated pseudomembranous colitis was first reported in 1978 by Bartlett and colleagues,[2,3] and although first reported in patients receiving clindamycin, *C difficile* infection (CDI) has been associated with antibiotic use in general with highest risk

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following the use of clindamycin, cephalosporins, and fluoroquinolones.[4] Furthermore, the combination of multiple antibiotics and longer duration of antibiotic use is associated with increased risk of developing CDI.[5] The continuation of any nonclostridia antibiotics after initial diagnosis has been shown to be associated with increased rates of recurrent disease.[6,7]

CDI is the most common cause of antibiotic-associated diarrhea and is defined as the acute onset of diarrhea with documented *C difficile* or its toxin, and no other identifiable cause for diarrhea.[8] Reports on incidence of this infection have shown that the incidence of CDI has nearly tripled between 1996 and 2005 from 31 per 100,000 to 84 to 112 per 100,000.[9,10] A more recent survey of US health care facilities from 2008 reported that among hospitalized patients the prevalence rate had continued increasing and was up to 13.1 per 10,000.[11] A 2008 study by Zilberberg and colleagues[10] analyzed CDI trends and stratified the data based on patient age; they noted that whereas adults ages 18 to 44 had an increased incidence from 1.3 to 2.4 per 10,000, the incidence of CDI in adults aged 65 to 84 increased from 22.4 to 49 per 10,000, and the incidence in adults aged greater than 85 also more than doubled from 52 to 112 per 10,000. It is estimated that nosocomial CDI increases the cost of hospitalization four-fold compared with matched cohorts and has been reported to cost between $3.2 and $4.8 billion per year.[12–14] In addition to increasing rates of prevalence, mortality rates associated with CDI have also been increasing significantly, rising from 5.7 per million in 1999 to 23.7 per million in 2004.[15]

Although CDI is frequently thought of in the inpatient setting, studies that have tested the stool of healthy adults found that 5% to 15% of healthy adults are carriers of *C difficile* and 40% of patients who develop community-acquired CDI go on to require subsequent hospitalization.[16–18] When the stool from patients requiring prolonged hospitalization was examined, the rate of colonization jumps significantly to 26% to 50%.[9,19–22] Most of these patients remain asymptomatic with one study, which examined 428 hospitalized patients, reporting a 26% colonization rate among hospitalized patients and that 62% of those patients remained asymptomatic throughout their hospital stay.[23] Overall, patients who develop symptomatic CDI typically have had antibiotic exposure within the past 3 months, have recently been hospitalized, and are older (typically defined as age >65). In addition to increased risk for CDI, advanced age has been shown to be associated with increased rates of recurrence, worse outcomes, and a 68% higher 30-day mortality compared with younger patients.[24,25]

BACTERIAL CHARACTERISTICS

Clostridium difficile is an obligate anaerobic gram-positive spore-forming bacterium that is transmitted via a fecal-oral route. To survive outside of its host and allow for transmission between hosts it produces endospores, which are metabolically inactive and therefore resistant to stomach acid and most classes of antibiotics. The bacterium is noninvasive and produces its pathology through the production of toxin A (a 308-kD enterotoxin) and toxin B (a 269-kD cytotoxin).[26] These toxins inactivate Rho GTPases and work in conjunction to open cellular tight junctions within the intestine leading to increased vascular permeability and inducing the production of tumor necrosis factor and inflammatory cytokines. Additionally, there is a neutrophil chemotactant influence. This results in an extensive inflammatory response and cellular necrosis, which in conjunction with actin depolymerization induced by cytotoxin results in the development of pseudomembranes. Some strains of *C difficile* have also been shown to produce an additional binary toxin, which some studies have reported as being