

# Overview of Severe *Clostridium difficile* Infection

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## KEYWORDS

- *Clostridium difficile* • *Clostridium difficile* colitis • Pseudomembranous colitis
- Nosocomial infection

## KEY POINTS

- *Clostridium difficile* infection constitutes a significant burden both to the individual patient as well as to the health care system in general.
- In recent years, there has been an increase not only in the incidence but also the severity of *C difficile*-associated disease.
- The management of patients with severe and fulminant *C difficile* infection presents a challenge for the critical care practitioner.
- Surgical intervention may be necessary for severe, and particularly for fulminant *C difficile* colitis.

## BACKGROUND

Complications associated with the use of antibiotics began to be recognized soon after their introduction into clinical practice. Antibiotic-associated diarrhea was noted to be a relatively common complication. A distinct type of antibiotic-associated diarrhea, characterized by colonic mucosal necrosis and the development of pseudomembranes came to be recognized as pseudomembranous colitis. In 1978, the bacterial-pathogen causing, antibiotic-associated pseudomembranous colitis was identified as *Clostridium difficile*.<sup>1</sup>

*C difficile* is an anaerobic, spore-forming, gram-positive bacillus. It is capable of causing a wide spectrum of disease, ranging from asymptomatic colonization to fulminant colitis requiring surgical intervention.<sup>2–5</sup> Morbidity rates associated with *C difficile* infection have been reported to be as high as 80%, with mortality rates of up to 8%.<sup>6,7</sup>

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The problem of *C difficile*-associated disease is growing worse rather than better. Of particular note, the severity of illness also seems to be increasing. Thus, knowledge of this disease, including its clinical manifestations, diagnosis, and potential treatment options is imperative in managing the critically ill patient population. Treatment is multifaceted, including pharmacologic therapy; supportive care; and, in a small number of patients, surgical intervention. Surgical consultation is particularly important in critically ill patients who have severe or fulminant *C difficile* colitis.

## EPIDEMIOLOGY

*C difficile* is the most common pathogen associated with nosocomial infectious diarrhea in hospitalized patients.<sup>8</sup> The overall incidence and severity of *C difficile*-associated disease seems to be increasing. From 1990 to 2000, the reported incidence of severe or fulminant *C difficile* colitis increased from 0% to 3.2%.<sup>9</sup> The increase in the number and severity of infections can likely be attributed to the emergence of more pathogenic strains, particularly the B1/NAP1/O27 strain.<sup>2-5</sup> This strain produces large amounts of *C difficile* toxins A and B, which are thought to mediate the disease process. In addition to significant morbidity and mortality, *C difficile* infection is associated with significant increases in hospital lengths of stay and costs.<sup>5,10</sup> In the United States, the costs were estimated to be approximately \$3.7 billion in 2003<sup>11</sup> and \$4.8 billion in 2008.<sup>12</sup>

*C difficile*-associated disease is usually a health care-associated infection, typically acquired during hospitalization.<sup>13,14</sup> The most common risk factor for acquisition of this disease is prior antibiotic exposure. The antibiotics most strongly implicated in this acquisition are clindamycin, cephalosporins, some penicillins, and fluoroquinolones; the latter are particularly associated with acquisition of the highly toxigenic B1/NAP1/O27 strain.<sup>3,6,15-19</sup> Other risk factors for *C difficile*-associated disease include age, immunosuppression, and possibly use of gastric acid-suppressing medications.<sup>16,20,21</sup>

## CLINICAL MANIFESTATIONS

Infection with *C difficile* can range from asymptomatic colonization to fulminant disease. The most common symptom of patients with *C difficile* infection is diarrhea; the number of bowel movements may be highly variable.<sup>22,23</sup> Patient may also have more acute symptoms, such as abdominal pain and cramping, which usually indicates somewhat more severe disease. Systemic signs of infection, such as fever and leukocytosis are also evidence of more severe disease. Some of these more severely ill patients manifest signs of severe sepsis, with evidence of organ dysfunction due to hypoperfusion, or frank septic shock, with evidence of hypotension.<sup>3,22,24</sup> In critically ill patients with severe sepsis or septic shock without an obvious source, infection with *C difficile* should be included in the differential diagnosis. It is important to realize that many of these critically ill patients will not present with diarrhea as a predominant symptom, because of severe colonic dysmotility induced by the infection.<sup>8</sup>

Because of the wide spectrum of clinical manifestations of *C difficile*-associated disease, several systems have been developed to stratify disease severity and provide some rationale for directing therapy. For the intensivist, it may be particularly important to recognize symptoms and signs of severe disease so that patients who would benefit from the care provided in an ICU are appropriately admitted to that facility. As mentioned above, greater severity of disease is associated with evidence of increasing hypovolemia and systemic signs of infection, with the greatest severity of disease (classified as fulminant or life-threatening) found in patients with catastrophic abdominal emergencies or signs of severe sepsis or septic shock. A stratification

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