

HOSPITAL PHYSICIAN®

INFECTIOUS DISEASES BOARD REVIEW MANUAL

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The *Hospital Physician Infectious Diseases Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

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Clostridium difficile–Associated Disease

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Clostridium difficile–Associated Disease

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INTRODUCTION

Clostridium difficile–associated diarrhea (CDAD) continues to be a major problem in hospitals and other health care facilities. The emergence of a new strain of *C. difficile*, typed as restriction endonuclease group BI, pulse field gel electrophoresis type NAP1, and toxinotype III (BI/NAP1), is particularly concerning. This strain produces 16 to 25 times the toxin of standard strains and has been associated with more severe disease and increased mortality.^{1,2} This article reviews the pathogenesis, epidemiology, clinical presentation, diagnosis, treatment, and prevention of CDAD with an emphasis on the new virulent BI/NAP1 strain.

PATHOGENESIS

First described by Hall and O'Toole³ in 1935, *C. difficile* is a spore-forming anaerobic gram-positive rod. It was identified as the cause of antibiotic-associated pseudomembranous colitis in 1978.^{4,5} When a susceptible host develops altered colonic flora related to contact with antibiotics or chemotherapy drugs and is exposed to *C. difficile* by fecal-oral transmission,^{6,7} acid-resistant *C. difficile* spores pass intact into the disrupted gastrointestinal tract where they germinate, proliferate, and release exotoxins A and B. Vegetative forms can transmit infection in achlorhydric patients.⁸

C. difficile toxins A and B adhere to receptors on the colonic epithelial cell brush border and cause colonic damage via inactivation of Rho proteins, resulting in actin filament disintegration, cytoskeleton disruption, and cell death.^{9–11} Toxin A also causes intestinal fluid secretion and promotes chemotaxis and inflammation with resultant pseudomembrane formation.¹² Although toxin B does not affect permeability, fluid secretion, or neutrophil migration, it is more potent than toxin A in damaging the human colonic mucosa.¹³

The recently described *C. difficile* strain, BI/NAP1, demonstrates a 16- to 23-fold increased production of toxins A and B compared with historical controls and

causes more severe disease.^{1,2} The increased toxin production is thought to be secondary to a partial deletion in the *tdc* gene, a down-regulator of toxins A and B.¹⁴ The BI/NAP1 strain also produces a binary toxin, but its role in pathogenesis is unclear.¹⁵

The pathologic appearance of the CDAD-affected colon ranges from normal to mild hyperemia to scattered ulcerations to diffuse pseudomembrane formation (**Figure 1**). Microscopically, when pseudomembranes are present, the mucosal surface contains ulcers with neutrophilic infiltrates and an overlying pseudomembrane (**Figure 2**).

EPIDEMIOLOGY

C. difficile can be found as part of the intestinal flora of 3% of healthy persons and in up to 20% to 40% of hospitalized patients. *C. difficile* has been implicated as the cause of 10% to 25% of antibiotic-associated diarrhea and 95% of pseudomembranous colitis. *C. difficile* has the ability to sporulate, which allows for its survival in a variety of harsh environments.^{16,17}

Over the past 10 years, many centers in the United States and Canada have reported increasing incidence and severity of CDAD in hospitalized patients. A U.S. hospital noted an increase from 6.8 cases/1000 discharges between 1989 and 1999 to 11.6 cases/1000 discharges in 2000.¹⁸ Hospitals in Quebec reported an increased incidence of CDAD from 35.6/100,000 population in 1991 to 156.3/100,000 in 2003.¹⁹ Data from the Centers for Disease Control and Prevention revealed that hospital discharge diagnosis of CDAD increased significantly from 31/100,000 population in 1996 to 61/100,000 in 2003.²⁰ The increased incidence was disproportionately higher in persons aged older than 64 years, with approximately 150 discharges/100,000 population in 1996 to more than 300 discharges/100,000 population in 2003. In addition, all-cause 30-day mortality following CDAD increased from 4.7% in 1991 to 13.8% in 2003, and 1-year attributable mortality has been reported as high as 17% in Canadian studies.^{19,21} Other studies have noted lower attributable mortality (1.5%) but elevated all-cause