CLINICAL UPDATE

Advances in *Clostridium difficile* From Digestive Disease Week 2016

Pathophysiology of *Clostridium difficile*–Associated Diarrhea

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Based on a Presentation From Digestive Disease Week 2016

G&H What are the clinical consequences of *Clostridium difficile*–associated diarrhea?

BY *Clostridium difficile*–associated diarrhea (CDAD) can be associated with a wide spectrum of signs and symptoms ranging from mild diarrhea to life-threatening complications. Gastroenterologists often see patients with mild to moderate disease, defined by the Infectious Disease Society of America in 2010 as diarrhea and leukocytosis with a white blood cell (WBC) count below 15,000 cells/mm^3 and a serum creatinine level less than 1.5 times the premorbid level. Severe CDAD involves leukocytosis with a WBC count of at least 15,000 cells/mm^3 or a serum creatinine level at least 1.5 times the premorbid level. Severe and complicated disease is associated with the presence of hypotension or shock, ileus, or megacolon. The 2013 American College of Gastroenterology (ACG) criteria incorporate albumin levels, with severe disease defined as a serum albumin level less than 3 g/dL plus a WBC count of at least 15,000 cells/mm^3 or abdominal tenderness. Severe and complicated disease includes a range of other events, including admission to the intensive care unit for *C difficile* infection, hypotension with or without use of vasopressors, fever at least 38.5° C, ileus or significant abdominal distention, mental status changes, a WBC count of at least 35,000 cells/mm^3 or less than 2000 cells/mm^3, a serum lactate level greater than 2.2 mmol/L, or end organ failure. The ACG criteria also describe other clinical manifestations of CDAD, including colitis, pseudomembranous colitis, fulminant colitis, small-bowel CDAD, and small-bowel disease, which have been well described in patients, particularly after colectomies and bacteremia.

G&H What is the typical disease course of CDAD?

BY Some patients go through a progression, whereas others present very rapidly. This is somewhat arbitrary; however, it is not uncommon to see patients with *C difficile* infection have WBC counts greater than 30,000 cells/mm^3, which are typically seen in patients who are rapidly heading toward the intensive care unit.

G&H How much of a health threat does *C difficile* infection currently pose?

BY *C difficile* poses an immediate, significant health care concern. Accordingly, the Centers for Disease Control and Prevention has designated *C difficile* infection as an urgent threat, defined as a high-consequence, antibiotic-resistant threat that has the potential to become widespread and, thus, requires urgent attention to identify infections and minimize transmission. This classification, which *C difficile* shares with carbapenem-resistant Enterobacteriaceae and drug-resistant *Neisseria gonorrhoeae*, requires more monitoring and infection-control studies. The threat of high consequence reflects the significant risks of *C difficile* infection that have been identified involving economic impact, clinical impact, incidence, and 10-year incidence projections. There are also issues pertaining to infection transmissibility. It is surprising how little has been done pertaining to prevention of initial contact.

G&H What is the epidemiology of CDAD in the United States?

BY The incidence and burden of CDAD in the United States are growing and significant. In 2011, there were an estimated 453,000 total cases of CDAD, including 83,000 cases of first recurrence of CDAD, and there were 29,300 deaths within 30 days of the CDAD diagnosis. Recurrence is common, occurring in approximately 25% of patients. This issue multiplies upon itself, increasing the prevalence of CDAD in the population.

Among patients with CDAD, the 180-day mortality rate is significantly higher among patients who develop recurrence vs those who do not (36% vs 26%; *P*=.001), suggesting that patients in whom the infection is not eradicated after an initial event are in a higher-risk group associated with greater morbidity and mortality in subsequent episodes.

G&H What is the current state of *C difficile* prevention?

BY A recent high-quality study from the Quebec Heart Institute showed that screening and isolating asymptomatic carriers could reduce the incidence of *C difficile* infection in hospital communities. In the study, approximately 5% of screened patients were found to be *C difficile* carriers. Isolating these patients was associated with a significant reduction in the incidence of *C difficile* infections and prevented an estimated 63% of expected cases, based upon comparisons with a control period (*P*<.001).

Primary prevention is also key. Infection-reducing measures include the correct use of ultraviolet light, the proper use of cleaning agents in hospital rooms, and other barriers of infection control, such as appropriate care when handling patients with known *C difficile* infection. In addition, patient transporters should wear gloves when handling patients with known *C difficile* infection. Transporters go from one stretcher to the next. It has been speculated that if this occurs repeatedly without proper handling and preventive sanitation in the same institution, it may cause numerous cases of CDAD; however, this has not been proven.

G&H What is currently understood about the pathogenesis of *C difficile* infection?

BY The pathogenesis of *C difficile* infection can be considered in 3 clinical phases: microbial suppression, collateral damage, and a window of vulnerability. The first phase involves suppression of the normal protective intestinal microbiota. This can occur as a result of antibiotics such as clindamycin, ciprofloxacin, cephalosporin, and fluoroquinolones. Subsequent ingestion of *C difficile,* which is ubiquitous, leads to germination of *C difficile* spores and growth of toxin-producing cells that change the gastrointestinal epithelium and invoke an immune response, leading to CDAD symptoms—the collateral damage.

Recent evidence suggests that not only groups of bacteria but also specific bacteria can play a role in *C difficile* pathogenesis. In one study, a single bacteria was associated with cachexia in severely ill patients.

The composition of normal intestinal microbiota confers multiple benefits, including supplementary vitamin production, metabolic activities, colonization prevention, and immune response stimulation. Disruption of the intestinal microbiota leads to decreased competition for limited resources and increased bacterial cell lysis, leading to release of consumable carbon sources. Bacteria in this fixed environment can become quite complex. This has been observed in *C difficile* infection, in which toxin C brings the bacteria into closer contact with the epithelium, possibly for a competitive advantage or to protect a food source.

The third phase of *C difficile* pathogenesis is the window of vulnerability for recurrence that occurs as a result of *C difficile* treatment. Antibiotics used for CDAD suppress both the *C difficile* and the endogenous protective flora. The period of vulnerability starts at the time of the subinhibitory levels of the CDAD antibiotics and ends with recovery of the intestinal microbiota. The infection can recur when *C difficile* spores in the gastrointestinal tract survive despite treatment with CDAD antibiotics. Until the normal gut flora recovers, the *C difficile* can bounce back almost faster than the normal flora microbiota, causing recurrence. Upon spore germination, toxin production from vegetative cells starts the cycle of CDAD symptoms and the need for treatment with CDAD antibiotics. The likelihood of recurrence increases with each subsequent episode.

G&H Can the risk of CDAD recurrence be reduced?

BY Mechanisms of CDAD recurrence are multiple and complex. Clearly, both the adaptive and innate immune responses contribute to recurrence. Until a specific agent is available, general nutrition support, including micronutrients, should be considered to support patients at risk. I use prebiotics and probiotics for adjunctive support, although no strong evidence supports these agents for reducing CDAD recurrence.

G&H What are the risk factors for CDAD?

BY Both host factors and environmental factors contribute to the risk of developing CDAD. Host factors include prior CDAD episodes, age over 65 years (likely

due to the lack of plasticity of the gut flora to insult), and immunocompromised status (eg, malignancy, administration of chemotherapy, and renal failure with known defective T-cell–mediated immunity and systemic inflammatory disease). Environmental factors include the use of concomitant systemic antibiotics and/or proton pump inhibitors. Some recent data have shown that gamma-aminobutyric acid (GABA) may increase failure following fecal microbiota transplantation for the treatment of CDAD. In addition, according to Dr Tor Savidge's presentation at Digestive Disease Week 2016, medications affecting GABA such as zolpidem tartrate increased the risk of acquiring *C difficile* infection 4.8-fold for inpatients who were given broad-spectrum antibiotics.

G&H What is a typical case of CDAD?

BY Overall, clinical studies show a propensity of *C difficile* infections in suburban settings affecting elderly women. However, the patients affected can vary based upon the setting in which they are receiving antibiotics. In an urban hospital, patients who acquire *C difficile* infection may be more likely to be young men and are more associated with trauma, including automobile accidents and gunshot events requiring multiple surgeries and antibiotics.

A typical case for a scenario of recurrence would be a 72-year-old woman with a prior history of CDAD who is admitted to the hospital from a nursing home after 3 days of watery diarrhea. At the time of admission, she is receiving antibiotics for an acute exacerbation of chronic bronchitis and she is taking a proton pump inhibitor for gastroesophageal reflux disease symptoms. Such a hypothetical scenario is commonly seen in nursing homes and highlights the recurrent symptoms seen in patients with *C difficile* infection.

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Suggested Reading

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