National estimates show that the incidence of *Clostridium difficile* infection (CDI) is inexcusably rising, and, in some parts of the United States, CDI has surpassed methicillin-resistant *Staphylococcus aureus* as the most common health care–associated infection. With the spread of increasingly virulent strains of *C. difficile* in recent years, it has also become clear that in vulnerable patients, CDI is associated with a high incidence of medical and surgical complications, added health care costs, and mortality. This does not bode well. An in-depth understanding of the epidemiologic features of CDI is essential to guide preventive efforts and optimize treatment strategies. In this issue of *Mayo Clinic Proceedings*, 2 articles aim to advance the field by reporting data on CDI risk factors, treatment, and outcomes.1,2

Although antibiotic drug exposure remains the major risk factor for CDI, recent studies have identified other factors that may potentially increase risk. Among these factors is gastric acid suppression, particularly with proton pump inhibitor (PPI) use. Although some studies have found PPI use to predispose patients to CDI, the results have not been consistent.1,5 In a recent study of *Mayo Clinic Proceedings*, Khanna et al1 undertook a population-based study of CDI cases from 1991 to 2005 using *International Classification of Diseases, Ninth Revision*, codes to identify CDI. Of the 385 patients with definite CDI, 140 (36%) were taking gastric acid suppressive medications: 23% were taking PPIs and 13% were taking histamine type 2 receptor blockers. In multivariable analyses adjusting for comorbid illnesses, gastric acid suppression was not associated with an increased risk of severe or severe-complicated infection. Note that the study population did not have a control group free of CDI. Patients with gastric acid suppression also were not more likely to experience treatment failure or recurrent disease than were those not taking gastric acid suppression medications. This is an area of active inquiry that deserves further investigation.

Advances have recently been made in the diagnosis of CDI. The most commonly used diagnostic test has been an enzyme immunoassay to detect toxin A, B, or both in the stool of patients with suspected CDI, with approximate reported sensitivity of 80% and specificity of 86%.3,6 The criterion standards for *C. difficile* testing, whether toxigenic culture or the toxin B cytotoxin assay, are laborious and time consuming. Recent studies have examined the utility of polymerase chain reaction (PCR) assays for diagnosing CDI.7,8 With a turnaround time of hours rather than days, this test is promising for a rapid diagnosis of CDI. Moreover, a meta-analysis of 23 studies that examined the performance characteristics of PCR compared with those of a toxigenic culture or cytotoxin assay found that PCR had a sensitivity of 87% to 94% and a specificity of 94% to 97%.9,10 These promising characteristics suggest that the PCR should be a test of choice for rapid, accurate diagnosis of CDI.

Renal disease poses an increased risk of CDI, especially recurrent disease.11 Reasons that have been put forth to explain this increased risk include the immune dysfunction that accompanies kidney disease, the higher frequency of antibiotic use, and frequent exposure to the health care system, in which *C. difficile* is a ubiquitous pathogen. However, the magnitude of risk and outcomes of CDI in this population have not been well quantified. In this issue of *Mayo Clinic Proceedings*, Keddis et al12 report analyses of a large national database of hospitalized patients, the National Hospital Discharge Survey, with the objective to compare rates of CDI in hospitalized patients with chronic kidney disease (CKD) with those without CKD. They also evaluated outcomes of CDI, comparing patients with CKD with and without CDI. Of the 162 million adult hospitalizations between 2005 and 2009, 5% had CKD. The CDI rate in patients with CKD was higher (1.49%) compared with that in the non-CKD population (0.71%) (P<.001). Patients with CKD undergoing dialysis were more likely to develop CDI than were patients without CKD and patients with CKD not undergoing dialysis. Outcomes for patients with CKD and CDI compared with those for patients with CKD only were also worse. A CDI in patients with CKD was associated with longer hospitalization, a higher likelihood of colectomy, discharge to a health care facility, and increased hospital mortality. The authors were not able to examine other risk factors and treatment characteristics in patients with and without CKD. This limitation notwithstanding, their data have important implications for manage-
ent and future research. First, the data suggest that a high index of suspicion be maintained for CDI in patients with CKD, especially those undergoing dialysis. Second, a high degree of vigilance should be exercised when treating patients with CDI, because the risk of complications is considerable. Third, every effort should be made to avoid unnecessary antibiotic drug use in this population so as not to compound the risk of CDI further.

Prevention and management of CDI are fraught with challenges.\(^1\) \(^3\) The mainstay of treatment for an initial episode is metronidazole; oral vancomycin is reserved for patients with moderately severe disease. Twenty percent to 40% of patients with an initial episode of CDI will experience a recurrence. Treatment of recurrent CDI is an area in which research is urgently needed. Khanna et al\(^1\) report the results of a comprehensive narrative review describing the epidemiologic features of CDI and the treatment options that exist or are under study. A variety of important observations come to light from this review. First, CDI is now being described in patients who have traditionally been considered to be at low or no risk for CDI. These patients include women during the peripartum period, those with community-acquired CDI without the usual risk factors, and children. Although the cause of this increased incidence of CDI in low-risk populations is unknown, it has been proposed that increased colonization in the community may be playing a role. Second, treatment of asymptomatic \textit{C difficile} carriers should not be undertaken since there is no evidence to suggest that this is a beneficial approach. Third, infection prevention strategies should include attention to environmental disinfection. Although many new promising technologies are on the market, such as chlorine-based agents, UV light disinfection, and vaporized hydrogen peroxide, few have been subjected to large-scale comparative trials to determine efficacy. Fourth, a new management option has become available for CDI in the form of fidaxomicin.

Fidaxomicin is a macrolyclic antibiotic with no systemic absorption and excellent in vitro activity against \textit{C difficile}. In clinical trials, response rates were similar with fidaxomicin and vancomycin, although significantly fewer patients in the fidaxomicin group had a recurrence (15% vs 25%; \(P = .05\)).\(^4\) Fidaxomicin is well tolerated, but its expense in the face of a response rate similar to that of vancomycin for initial CDI makes its use a daunting proposition for many patients. There is a paucity of data to determine which patients with an initial episode of CDI are likely to have a recurrence; it is for this group that fidaxomicin may be most useful.

Fifth, local microbiota transplant has experienced a resurgence of interest as the population with recurrent CDI continues to grow. A recent systematic review of case series found an overall success rate of 92%. However, there was considerable variability in the way the fecal transplant was delivered; the various options included enemas, nasogastric instillation of a stool slurry, and colonoscopy. A randomized trial to compare the efficacy of fecal transplant with vancomycin taper for recurrent disease is under way, and the results are eagerly awaited.

Finally, additional available therapeutic options for recurrent CDI are limited but include rifaximin, cholestyramine, intravenous immunoglobulin, monoclonal antibodies, and probiotics. Of these, monoclonal antibodies were tested in a randomized controlled trial and were found to substantially reduce CDI recurrence.\(^1\) \(^5\) Additional trials are ongoing to further examine this promising therapy. Probiotics have not been studied rigorously, to my knowledge, as adjunctive treatment for CDI; thus, research in this area is needed. Probiotics are beneficial for the prevention of antibiotic drug–associated diarrhea and are widely used for this indication; whether they have a role to play in the primary prevention of CDI is another area ripe for research.

**REFERENCES**


