Antibiotic-Associated Diarrhea and *Clostridioides difficile* Infection

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CHAPTER OUTLINE

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**ANTIBIOTIC-ASSOCIATED DIARRHEA**

**Etiology**

Diarrhea is a common adverse effect of antibiotic use and can result from a variety of mechanisms. The most common type of diarrhea, often simply called *antibiotic-associated diarrhea* (AAD), is not associated with any specific pathogen and is, in fact, not the result of infection; it is believed to be caused by a disturbance of the normal colonic microbiota that leads to alterations in the bacterial metabolome. Such metabolic changes include alterations in the degradation of nonabsorbed carbohydrates, leading to osmotic diarrhea; decreased bile salt deconjugation by bacteria leading to stimulation of fluid secretion by the colonic mucosa; reduced bacterial degradation of bile salts, which increase intestinal permeability, increase cyclic adenosine monophosphate (cAMP), activate mast cells, and stimulate colonic chloride secretion (see Chapter 101); stimulation of intestinal motility through the motilin-like effect of erythromycin; an allergic reaction; or infection with microorganisms other than *C. (Clostridioides) difficile*, including *Clostridium perfringens* type A, *Staphylococcus aureus*, and *Salmonella enterica*.2,4

The genotype of *C. perfringens* that causes AAD is distinct from those that induce food poisoning.1,3 Type A strains isolated from patients with AAD carry the *C. perfringens* enterotoxin gene in a plasmid, whereas those that cause food poisoning have a chromosomal *C. perfringens* enterotoxin gene. *S. aureus* was identified as a cause of severe AAD and enterocolitis before *C. difficile* was identified.2,4 Since the advent of sensitive and specific testing for *C. difficile*, however, very few cases of *S. aureus* AAD have been confirmed, and the true role played by this pathogen in AAD is unclear. *Klebsiella oxytoca* is another pathogen that releases several potent toxins and causes AAD associated with right-sided hemorrhagic colitis.7

AAD complicates 2% to 25% of antibiotic treatment courses, but the incidence varies depending on the antibiotic used; it is more common, for example, during therapy with ampicillin (5% to 10%), amoxicillin-clavulanate (10% to 25%), or cefixime (15% to 20%) and less common during therapy with fluoroquinolones (1% to 2%) or trimethoprim-sulfamethoxazole (<1%).8

Most cases of AAD are mild, self-limited, and unaccompanied by fever. Pseudomembranous colitis is absent, and significant complications are rare. *C. difficile* (CDI) accounts for less than 10% of AAD cases but is an important pathogen to identify because it often requires specific antimicrobial therapy and can lead to life-threatening complications, as discussed later. A comparison between the clinical features of AAD caused by *C. difficile* and AAD from other causes is presented in Table 112.1.9

**Prevention and Treatment**

Management of AAD consists of discontinuing the inciting antibiotic if possible. If the diarrhea is moderately severe or poorly tolerated, an antiperistaltic agent (e.g., loperamide) or bismuth subsalicylate may be used to relieve symptoms.

Because AAD is believed to result from an alteration of the normal colonic microbiome, a variety of probiotic agents has been evaluated for its treatment and prevention (see Chapter 130). In a double-blind controlled clinical trial, oral capsules containing viable *Saccharomyces boulardii*, a nonpathogenic yeast, were coadministered with antibiotics; this combination treatment reduced the incidence of AAD in hospitalized patients from 22% in the placebo group to 9.5% in the *S. boulardii* group (*P* = 0.04).10 Another randomized placebo-controlled trial, however, failed to demonstrate a beneficial effect for *S. boulardii* in an older adult population of antibiotic recipients.11 *Lactobacillus* species, in particular *Lactobacillus rhamnosus* GG, also have been studied in clinical trials of AAD. In one study of children being treated for respiratory tract infections, *Lactobacillus* GG was effective in reducing the incidence of AAD to 3% compared with a 16% incidence in the placebo group12; other clinical trials of *Lactobacillus* GG have yielded negative results.13 A meta-analysis examined the results of randomized double-blind placebo-controlled trials of probiotic therapy for AAD published between 1966 and 2000.14 Nine studies were analyzed, including 4 using *S. boulardii* and 4 using *Lactobacillus* GG. The combined odds ratio (OR) for AAD in the probiotic-treated groups was 0.37 compared with placebo (95% confidence interval [CI]: 0.26–0.53; *P* < 0.001). For *S. boulardii*, the OR in favor of active treatment over placebo was 0.39 (95% CI: 0.25–0.62; *P* < 0.001) and for lactobacilli the OR was 0.34 (95% CI: 0.19–0.61; *P* < 0.01). A recent systematic review and meta-analysis also examined the comparative efficacy and tolerability of probiotics for AAD. The authors found that *L. rhamnosus* GG (LGG) had the highest probability of being ranked best both in effectiveness (OR, 95% CI = 0.28 [0.17–0.47]) and tolerance (0.44 [0.23–0.84]) for prevention of AAD. In summary, the weight of published evidence suggests that probiotic agents such as LGG and *S. boulardii*, when used prophylactically in combination with antibiotics, reduce the risk for AAD. Such therapy may be especially advantageous in patients with a history of susceptibility to troublesome AAD.

**PSEUDOMEMBRANOUS ENTEROCOLITIS**

Pseudomembranous enterocolitis was a rare entity in the medical literature before the widespread use of antibiotics. In recent
decades, however, pseudomembranous colitis has emerged as a common complication of antibiotic use, with almost all cases caused by infection with toxin-producing strains of *C. difficile*.

A case report by Finney, published in 1893, is considered to be the first description in the medical literature of pseudomembranous enterocolitis. In that instance, fatal pseudomembranous inflammation of the small intestine followed surgery in a debilitated young woman with gastric outlet obstruction caused by peptic ulcer disease. The presence of an inflammatory pseudomembrane overlying intestinal mucosa characterizes pseudomembranous colitis (when the colon alone is involved) or pseudomembranous enterocolitis (when the small intestine also is involved). The pseudomembrane consists of inflammatory and cellular debris and forms distinctive patches of yellow or whitish-gray exudate that obscure the mucosa underlying them. In early lesions, a 1 to 2 mm area of punctate ulceration may be visible. Grossly, pseudomembranes consist of ovoid plaques of 2 to 10 mm in diameter separated by areas of normal or hyperemic mucosa. Histologically, pseudomembranes can be seen to emanate from central areas of epithelial ulceration and erupt from the intestinal/colonic crypts in a “volcano-like” fashion. In more severe cases, the areas of ulceration and the overlying pseudomembranes coalesce to cover large areas of mucosa.

Risk factors for the development of pseudomembranous enterocolitis in the absence of CDI include intestinal surgery, intestinal ischemia, and other enteric infections. During the 1940s to the 1970s, most reported cases of pseudomembranous enterocolitis occurred following abdominal or pelvic surgery. Bartlett has identified descriptions of pseudomembranous enterocolitis in the medical literature associated with a wide variety of other intestinal disorders, including Shigella infection, Crohn disease, neonatal necrotizing enterocolitis, intestinal obstruction, Hirschprung disease, and colonic carcinoma. Intestinal ischemia can result in histologic changes similar to those observed in severe *C. difficile* colitis, although classic pseudomembranes are uncommonly seen. Severe systemic insults including shock, advanced renal failure, spinal fracture, extensive burns, heavy metal poisoning, and hemolytic-uremic syndrome also have been associated with pseudomembranous enterocolitis. A potential common etiologic factor shared by many of these disorders is hyperperfusion of the intestinal mucosa with resultant ischemic necrosis and ulceration.

Infectious agents other than *C. difficile* have been implicated as causes of pseudomembranous colitis, most notably *S. aureus*. Before *C. difficile* was identified as the most common cause of pseudomembranous colitis, *S. aureus* often was identified in stool cultures of patients with postoperative pseudomembranous enterocolitis, and oral vancomycin proved to be effective therapy. In retrospect, however, it is difficult to ascertain whether the efficacy of vancomycin reflected its activity against staphylococcal infection or against unrecognized infection with *C. difficile*.

*Clostridium difficile*, recently reclassified as *Clostridioides difficile*, is an anaerobic, gram-positive, spore-forming, toxigenic bacillus, first isolated in 1935 from the fecal flora of healthy neonates. The organism then passed into obscurity until 1978, when the association between toxins released by *C. difficile* and antibiotic-induced pseudomembranous colitis was first reported. Since that time, the incidence of CDI has increased dramatically, and the organism is now recognized as the primary cause of nosocomial infectious diarrhea in developed countries. The reported incidence of CDI has risen substantially over the past 2 decades. For example, in the USA, the Agency for Healthcare Research and Quality identified 127,580 reported cases of CDI in hospitalized patients in 1997, 246,139 cases in 2004, and 346,805 cases in 2010. Reported deaths from CDI in the USA rose from 793 in 1999 to 7483 in 2008. Similarly, in the UK, the number of *C. difficile*-related deaths in the UK had fallen dramatically to 19 per million population.

CDI also appears to be accompanied by heightened morbidity and mortality, owing in part to the emergence of increasingly virulent strains. One such strain was initially identified in the 1980s by restriction endonuclease analysis and named BI, but currently is referred to as North American Pulsed Field type 1 (NAP-1) or as PCR ribotype 027. The NAP-1 strain has led to severe outbreaks of CDI, with high mortality rates in both North America and Europe. The NAP-1 strain also produces binary toxin in addition to toxins A and B (see under “*C. difficile* toxins”) and shows high level resistance to fluoroquinolones, making it more prevalent in patients receiving this class of antibiotics.
Epidemiology

Intestinal carriage rates of *C. difficile* in healthy adults are low (0% to 3% in American and European populations) and might represent intestinal transit without true colonization. In contrast, hospital inpatients treated with antibiotics have reported colonization rates of 10% to 21%. Acquisition from the hospital environment is a major source of CDI, not only from infected stool but also via environmental surfaces including floors, call buttons, soiled bedding, bedrails, and toilet seats. One study demonstrated that spores persisted in toilets after flushing 24 times. The hands and stethoscopes of health care workers are also potential sources of nosocomial CDI. In one study, 29% of environmental cultures were positive for *C. difficile*, compared with only 8% of cultures from rooms of patients who were culture-negative for *C. difficile*. In antibiotic-treated animals, the infective dose of toxigenic *C. difficile* may be as low as 2 organisms. If human susceptibility is similar, control of CDI in hospitals will continue to be a major challenge because up to 10⁶ organisms per gram of stool are excreted in liquid feces. Highly resistant spores of *C. difficile* can persist for many months in the hospital environment and can result in infection if ingested by a susceptible host.

Although it is not possible to eradicate *C. difficile* and its spores from the hospital environment, certain control measures have been recommended to reduce the prevalence of *C. difficile*-associated diarrhea (Box 112.1). Infected patients should be bedded in private rooms whenever possible to reduce patient-to-patient spread of *C. difficile*. Strict precautions including use of gowns and gloves and regular hand washing after patient contact should be observed. The use of alcohol-based hand gels may not be as effective as washing with soap and running water in removing *C. difficile* spores; hence, washing with soap and running water is recommended as an additional measure in an outbreak setting. A controlled trial of using vinyl disposable gloves during patient contact also reduced the transmission of infection. After discharge of infected patients, surface environmental disinfection is best performed with a cleaning agent (e.g., hypochlorite solution) that contains approximately 5000 ppm available chlorine (corresponding to a 1:10 dilution of household bleach). Ultraviolet light-based cleaning also has been shown to be effective against CDI spores and is being adapted in hospitals to clean patients’ rooms after discharge.

Hospital outbreaks of *C. difficile*-associated diarrhea are common and likely result from the close approximation of susceptible persons (older and infirm patients) who are taking antibiotics and who are then exposed to the pathogen either in the hospital environment or through direct person-to-person spread. Outbreaks of infection are seen with the emergence of virulent strains, which are highly toxigenic and resistant to numerous antibiotics including fluoroquinolones. CDI is best prevented by avoiding the unnecessary use of broad-spectrum antibiotics, especially in hospitalized patients, and by careful attention to hand hygiene and environmental cleaning.

CDI may be hospital or community acquired. Hospital-acquired infections may have their onset of symptoms and signs of colitis develop in the hospital or after discharge to the community. The reported incidence of community-acquired CDI (8 to 12 cases per 100,000 person-years) is substantially lower than that of hospital-acquired CDI, but has increased in recent years. Community-acquired CDI is often diagnosed in patients who lack typical risk factors for the disease (e.g., recent antibiotic exposure). In a recent population-based study, community-acquired CDI accounted for 41% of total cases; patients with community-acquired disease were more likely to be younger women with less comorbidity and likelihood of antibiotic exposure compared with individuals who had hospital-acquired disease.

Pathogenesis

The pathogenesis of CDI usually requires alteration of the normal colonic microflora; oral ingestion of *C. difficile* spores; colonization of the large intestine; production and release of toxins A and B into the colonic lumen; binding and internalization of toxins by colonocytes and lamina propria inflammatory cells;
and subsequent colonic damage (colitis). Several host factors, particularly the immune response to *C. difficile* toxins, determine whether a patient remains an asymptomatic carrier or develops colitis (Fig. 112.1).

**Alteration of the Colonic Microbiota**

CDI usually follows antimicrobial therapy, other events such as treatment with chemotherapy agents, or association with certain diseases such as IBD, all of which have related perturbations in the colonic microbiota. A diverse and phylogenetically rich microbiota is protective against CDI, especially recurrent CDI (see later). The protective barrier provided by the normal intestinal microbiota is often referred to as colonization resistance; its impairment by antibiotics and subsequent infection with *C. difficile* can be demonstrated in animal models.86–89 *C. difficile* also can colonize the intestines of germ-free mice but is eliminated after these animals are inoculated with feces from normal mice, clearly confirming the importance of germ-free mice but is eliminated after these animals are inoculated with feces from normal mice, clearly confirming the importance of

Human neonates have poor colonization resistance because they have not yet developed a stable complex colonic microbiota.91 Colonization rates with *C. difficile* of 25% to 80% have been reported in healthy infants and children up to 24 months of age, who, despite large concentrations of toxins in the feces, rarely develop *C. difficile*–associated diarrhea. Absence of toxin receptor expression on the immature colonic epithelium has been suggested as a mechanism to explain the symptomless carrier state in infants and children.92

Almost all antimicrobial agents can predispose to CDI; certain classes, specifically third- and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and clindamycin, currently carry the highest risks (Table 112.2).25,32,35–37 Cancer chemotherapeutic agents or bowel preparation regimens (e.g., before colonoscopy or colonic surgery) rarely result in sufficient disturbance of the intestinal microbiota to allow subsequent colonization with *C. difficile*.38

**C. difficile** Toxins

Pathogenic strains of *C. difficile* produce 2 structurally similar protein exotoxins, namely, toxin A and toxin B, which are the major known virulence factors. The genes encoding toxin A and toxin B reside in a 19.6-kb chromosomal region, the *C. difficile* pathogenicity locus, which contains the genes encoding toxin A (*tcdA*) and B (*tcdB*) as well as 2 putative regulatory genes (*tcdC* and *tcdD*, also called *tcdR*) (Fig. 112.2).59,60 The *tcdB* gene product appears to up-regulate toxin transcription by complexes with RNA polymerase that binds to the toxin promoter regions. The *tcdA* gene is transcribed in the opposite direction to *tcdA*, *tcdB*, and *tcdD*, and its gene product appears to decrease toxin production.59,60 The 5th gene of the pathogenicity locus, *tcdE*, encodes a protein with sequence similarity to bacteriophage pore-forming holin proteins and mediates the secretion of *C. difficile* toxins across the bacterial cell membrane.64,65

Toxins A (308 kd) and B (220 kd) are members of the large clostridial cytotoxin family; they share a number of structural features, and are 49% identical at the amino acid level.66–68 Both toxins carry an N-terminal enzymatic domain that mediates their toxic effects on mammalian cells, a central hydrophobic region that might act as a transmembrane domain to facilitate entry into the cytoplasm, and a C-terminal domain consisting of a series of repeated sequences that mediate toxin binding (Fig. 112.3).69 A fourth domain also has been identified, which encodes an intrinsic peptidase that releases the N-terminal enzymatic domain into the cytosol.69

Both toxins function as uridine diphosphate glucose hydrolases and glucosyltransferases, a requirement for their cellular toxic effects. Following internalization into the host cell cytoplasm, the toxins catalyze the transfer of UDP-glucose to the toxins, leading to the release of proinflammatory cytokines including interleukin (IL)-1β, TNF-α, and IL-8.69,70 These cellular proinflammatory effects contribute to the marked intestinal inflammatory response evident in *C. difficile*–associated diarrhea and pseudomembranous colitis.

Toxin A initially was thought to be the only enterotoxin based on studies in animals,69,71,72 whereas toxin B, an extremely potent cytotoxin, appeared to have little independent enterotoxic activity in animals. This suggested that toxin B did not contribute to diarrhea and colitis in humans.71,73 This view was challenged by studies on human colon showing that, in fact, toxin B is 10 times more potent than toxin A in inducing in vitro colonic injury.74,75 Furthermore, toxin A+/toxin B− strains of *C. difficile* have been

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**Table 112.2** Antimicrobial Agents That Predispose to CDI

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<th>Frequent</th>
<th>Sometimes</th>
<th>Rarely</th>
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<td>Amoxicillin</td>
<td>Macrolides</td>
<td>Aminoglycosides</td>
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<td>Ampicillin</td>
<td>Other penicillins</td>
<td>Bacitracin</td>
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<tr>
<td>Cephalosporins</td>
<td>Sulphonamides</td>
<td>Carbenems</td>
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<td>Clindamycin</td>
<td>Trimethoprim</td>
<td>Chloramphenicol</td>
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<td>Fluoroquinolones</td>
<td>Trimethoprim</td>
<td>Daptomycin</td>
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<td></td>
<td>$\alpha$-sulfamethoxazole</td>
<td>Metronidazole</td>
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<td>Rifampin</td>
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<td></td>
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<td></td>
<td></td>
<td>Tetracyclines</td>
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<td>Tigecycline</td>
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isolated from patients with diarrhea and pseudomembranous colitis, confirming that toxin B is a major virulence factor in human disease. A minority (≈15%) of C. difficile clinical isolates produce a third toxin—binary toxin—that is analogous to the iota toxin of C. perfringens and is encoded at a site distant from the pathogenicity locus that encodes toxins A and B.30,31 Binary toxin is composed of 2 parts: a 48-kd enzymatic protein and a 99-kd binding protein. Although binary toxin shows some enterotoxic activity in animal models, its role in the pathogenesis of C. difficile–associated diarrhea and colitis remains unclear. Most pathogenic strains of C. difficile lack binary toxin but nonetheless cause substantial colonic inflammation and injury. The NAP-1 strain is binary toxin positive, however, thereby raising renewed suspicion that this toxin might enhance the pathogenic effects of toxins A and B.26,30

**Immune Response to C. Difficile**

Serum IgG and IgA antibodies against C. difficile toxins are found in >50% of healthy children and adults.77–81 Mucosal IgA antitoxin antibodies also are detectable in colonic secretions from >50% of humans and might inhibit receptor binding of toxin A.79,81 Immunization against C. difficile toxins protects animals from C. difficile colitis but does not protect against colonization—a situation that may be similar to the asymptomatic carrier state in humans.16,82

High concentrations of antitoxin antibody in the serum are associated with protection against CDI,83–85 whereas recurrent CDI has been associated with low serum antitoxin antibody levels in children and adults.77,81,86,87 In one study, adult inpatients with C. difficile diarrhea and a low concentration of serum antitoxin had a 48-fold greater risk of recurrent disease after initial successful treatment compared with patients who had high antitoxin concentrations (Fig. 112.4).16,88 High serum antitoxin concentrations also have been identified in asymptomatic carriers of toxigenic C. difficile.16 In a prospective study of nosocomially-acquired C. difficile, 51% of infected patients who were asymptomatic carriers had serum IgG antitoxin A concentrations that were 3 times higher than those in patients with diarrhea (see Fig. 112.4).16 The immune response to toxin B has also been correlated with clinical outcomes, including risk of recurrence.84,85,88

**Other Risk Factors For CDI**

In addition to antimicrobial therapy and inpatient care, increasing age and increased comorbidity are important risk factors for CDI.30 The U.S. Agency for Healthcare Research and Quality has reported an overall CDI rate in hospitalized patients of 110 per 100,000 population. Age was a major risk factor for infection, with rates of 1089 per 1,000,000 population in those aged 85 or older compared with 486 per 1,000,000 for those 65 to 84 years of age, 101 per 1,000,000 for those 45 to 64 years of age, and 28 per 1,000,000 for those 18 to 44 years of age. Older adults are particularly predisposed to infection with C. difficile because of increased nosocomial antibiotic exposure and reduced innate and adaptive immune function. In one study of antibiotic recipients, patients with severe underlying disease at the time of hospital admission were 8 times more likely to develop CDI compared with patients who were less severely ill.16 Other reported risk factors for CDI include the use of an NG tube, GI procedures that are associated with bowel cleansing, ileus or both, ICU stay, and length of hospital stay.90 The strengths of the associations of these risk factors with C. difficile vary from study to study. These factors are often markers of disease severity, older age, or both, and the significance of their association with C. difficile can decline or be lost after controlling for these confounding variables.16,89,91

There is a dose-dependent association between acid suppression and risk for C. difficile–associated diarrhea.92,93 Although many studies have confirmed this association, others have found that the initial apparent association was lost after adjusting for confounding variables, and meta-analyses disagree as to the strength of evidence for a primary association between PPI use
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and risk for CDI and whether or not a cause-effect relationship might exist.\textsuperscript{94-96} \textit{C. difficile} spores are acid resistant; hence, potential effects of PPI use on CDI risk more likely result from microbiota alterations.

Patients undergoing cytotoxic chemotherapy for malignancy are at risk for CDI because of frequent antibiotic use, nosocomial exposure to \textit{C. difficile}, and severe comorbidity.\textsuperscript{97,98} Even in the absence of antibiotic use, antineoplastic chemotherapy predisposes to CDI, reflecting the ability of these drugs to alter the colonic microbiota and reduce \textit{C. difficile} colonization resistance.\textsuperscript{53} \textit{C. difficile}–associated diarrhea also has been reported in patients undergoing immunosuppressive therapy in the setting of solid organ or bone marrow transplantation.\textsuperscript{99,100}

Infection with a broad range of enteric pathogens including \textit{C. difficile}, \textit{Campylobacter}, and \textit{Salmonella} species can precipitate or mimic disease relapse in IBD. Patients with HIV infection are at risk for \textit{C. difficile}–associated diarrhea because of multiple risk factors, including frequent prophylactic and therapeutic antibiotic use, hospitalization, and immunodeficiency.\textsuperscript{101} \textit{C. difficile} colitis behaves the same in HIV-infected patients as it does in control groups,\textsuperscript{102} and testing for \textit{C. difficile} should be a routine part of the diagnostic evaluation in patients with diarrhea and a history of current or recent antibiotic treatment.

**CDI in IBD**

Another nonantibiotic risk factor for CDI is IBD. \textit{C. difficile} is the most commonly identified specific pathogen in IBD patients in North America and Europe, and is present in as many as 5% to 19% of patients with relapse of colitis in some case series.\textsuperscript{103-106} Patients with Crohn disease or UC remain at an increased risk of primary and recurrent CDI even in the absence of antibiotic or immunosuppressant therapy, likely caused by an underlying microbial dysbiosis associated with colitis.\textsuperscript{103-107} Patients who present with a flare of IBD should routinely be tested for CDI.\textsuperscript{108} IBD patients with CDI should be treated as having severe CDI even in the absence of severity markers such as leukocytosis or

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Fig. 112.3 Structure and function of \textit{C. difficile} toxins. Toxin A and toxin B share similar domains: a C-terminal binding domain (green) that is composed of contiguous repeating units also known as \textit{clostridial repetitive oligopeptides}; a central, major hydrophobic region (red oval) of 172 amino acids that is highly conserved and acts as a transmembrane domain; an intrinsic protease domain (pink); and an N-terminal enzymatic domain (light green) that carries the consensus DXD (aspartate-any intervening amino acid-aspartate) glucosyltransferase domain and is responsible for cytotoxicity. Interaction of the toxin B binding domain (green) with cell-surface receptors (dark blue) induces receptor-mediated endocytosis. The acidic pH of the endosome triggers the first conformational change and results in pore formation by the hydrophobic, translocation domain (red oval). Within the cytosol, a second conformational change activates intrinsic protease activity (pink). Autocatalytic cleavage of toxin B releases the catalytic glucosyltransferase domain (light blue) into the cytosol. Glucosylation of the cytosolic target Rho GTPase at a conserved threonine residue (Thr) leads to disaggregation of the cytoskeleton and cell death (see text for greater detail). Glc, \(\delta\)-glucose; UDP, uridine diphosphate. (Modified from Kelly CP, Lamont JT. \textit{Clostridium difficile}—more difficult than ever. N Engl J Med 2008; 359:1932-40.)
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Elevated creatinine; hence, they should be treated with vancomycin or fidaxomicin instead of metronidazole. Because CDI in IBD is associated with an increased risk of several adverse events including hospitalization, surgery, escalation of IBD therapy and mortality, one should consider hospitalization for monitoring and for the aggressive management for IBD patients with CDI who have profuse diarrhea, severe abdominal pain, a marked leukocytosis or evidence of sepsis. It may be prudent to postpone escalation of glucocorticoids and other immunosuppressive agents during acute CDI until therapy for CDI has been initiated because glucocorticoid escalation may be associated with worse outcomes. The decision to withhold, continue or escalate immunosuppression in IBD patients with CDI should be individualized because there is insufficient existing robust literature to guide firm recommendations. Like other patients with CDI, if diarrhea or other symptoms of colitis persist or return after antibiotic treatment, patients should be tested again for CDI. It may be hard to distinguish colonization from active infection if sensitive nucleic acid amplification testing (NAAT) is used owing to the possibility of more than one cause of symptoms, and it may be better to use a 2-step testing approach that includes a toxin assay in this situation. Lastly, IBD patients with recurrent CDI should be offered IMT because this treatment has been shown to be safe and effective to treat CDI in this patient population (see later).

Clinical Features

Clinical manifestations of CDI range from asymptomatic carriage to mild or moderate diarrhea to life-threatening pseudomembranous colitis with toxic megacolon. Asymptomatic carriage of C. difficile is common in hospitalized patients. Several large epidemiologic studies indicate that 10% to 21% of hospital inpatients receiving antibiotics in high-risk units are carriers. Although most of the C. difficile isolates from carriers are toxin producing, carriers do not develop symptomatic disease, perhaps as a result of adaptive protective immunity.

In patients who develop diarrhea with C. difficile, symptoms usually begin soon after colonization. The incubation period is usually less than a week, with a median time of onset of approximately 2 days. Colonization can occur during, or for up to 2 or even 3 months after, antibiotic treatment.

C. difficile diarrhea is typically associated with the frequent passage of loose or watery bowel movements. Some patients present with fever, leukocytosis, and cramping abdominal pain. Mucus or occult blood may be present, but melena or hematochezia is uncommon and, if present, suggests IBD, colon cancer, or another source of bleeding. Because C. difficile is not an invasive pathogen, extraintestinal manifestations of CDI such as septic arthritis, bactereemia, or tissue abscesses are extremely rare. An oligoarticular, asymmetrical, nondeforming large-joint arthropathy, similar to that seen in other infectious colitides, is sometimes seen.

Patients with more severe disease can develop colonic ileus or toxic dilatation and present with minimal or even no diarrhea. In the absence of diarrhea, the only clues to the diagnosis may be high fever, moderate or marked (e.g., leukemoid) polymorphonuclear leukocytosis, lower or diffuse abdominal pain, tenderness, and distention.

Abdominal plain films might reveal a dilated colon, toxic megacolon, or small bowel ileus with air-fluid levels mimicking intestinal obstruction or ischemia. In such cases, a CT scan of the abdomen may reveal nonspecific features common to ischemic, infectious, and inflammatory colitides (Fig. 112.5). Radiologic features of pseudomembranous colitis include mucosal edema, a thickened colonic wall, pancolitis, and pericolonic inflammation with or without ascites, and usually without small bowel involvement other than ileus; one notable exception is in patients with a mature ileostomy or ileal pouch where C. difficile can infect the colon-like altered ileal mucosa. Flexible sigmoidoscopy or colonoscopy is sometimes indicated to identify pseudomembranous colitis when the diagnosis remains unclear after initial evaluation (see later).

Complications of severe C. difficile colitis include dehydration, hypoalbuminemia, ascites, electrolyte disturbances, renal failure,
Diagnosis

The diagnosis of CDI is based on the presence of diarrhea plus other evidence of acute colitis, and demonstration in stools of *C. difficile* toxins or toxinogenic *C. difficile*. Although a history of recent antibiotic use is common, it is not a requirement for diagnosis as CDI is often seen without recent antibiotic exposure.

Whom to Test?

The diagnosis of CDI should be considered in a patient with acute diarrhea, especially if they had antibiotic exposure within the previous 2 to 3 months. Most, but not all, cases occur during or after hospitalization, although a significant proportion are community acquired. Approximately 40% of patients with CDI at tertiary referral centers are symptomatic on admission; most have had a recent hospitalization.

Recent CDI testing guidelines recommend that if there are pre-specified institutional criteria to test only stools from patients with unexplained and new onset diarrhea (3 or more unformed stools in 24 hours), then a NAAT can be used alone (Fig. 112.6). If these testing criteria are not in place, then a 2-step test starting with glutamate dehydrogenase (GDH) enzyme immuno-assay (EIA) or NAAT followed, if positive, by toxin testing (e.g., by EIA) is recommended (see later).

Whom Not to Test?

Testing of solid or formed stools for *C. difficile* toxin is not recommended because only patients with diarrhea require treatment. Patients who are not having diarrhea but test positive for *C. difficile* are considered as asymptomatic carriers. Treatment of asymptomatic carriers with antimicrobial agents against *C. difficile* is not recommended because it might prolong the carrier state beyond the usual 2 to 6 weeks.

Follow-up stool testing to confirm cure also is not indicated in an asymptomatic patient, even in patients discharged to chronic care facilities, because asymptomatic carriage is already highly prevalent in these facilities. Moreover, stool carriage of *C. difficile* can persist for up to 6 weeks after cessation of symptoms and does not require therapy. Because asymptomatic carriers can act as hidden reservoirs for CDI, especially in hospitals and nursing homes, universal precautions should be followed for all patients to reduce the likelihood of patient-to-patient spread of nosocomial infectious disease.

How to Test?

If CDI is suspected, a freshly passed stool sample should be submitted immediately to the laboratory in a clean, watertight container. Anaerobic storage or the use of transport media, such as Cary Blair medium, is not necessary. Storage of stool at ambient temperatures can result in denaturation of fecal toxin or bacterial DNA; samples should therefore be tested immediately or refrigerated or frozen, pending later testing.

A variety of laboratory tests are available to diagnose infection with toxinogenic *C. difficile* (Table 112.3). NAATs such as PCR are increasingly being used because of their high sensitivity. EIAs to detect toxin antigens in stool are also available and have the advantages of being relatively inexpensive, quick to perform (2 to 12 hours), and specific; however, their relatively low sensitivity can lead to false-negative results. The tissue culture cytotoxicity assay also is sensitive and has high diagnostic accuracy, but it is
more resource intensive and time consuming (24 to 72 hours). Anaerobic culture followed by determination of toxin production is both sensitive and specific; however, it requires specialized resources and expertise, and results take several days to obtain, leading to it being used in epidemiology studies but seldom in clinical practice.

**Enzyme-Linked Immunoassays**

Commercially available EIAs are widely used to detect toxins A and B of *C. difficile* in stool specimens. Toxin is detected by its interaction with either a monoclonal antibody or polyclonal antisera that specifically recognizes toxin epitopes. EIAs are easier to perform than the cytotoxicity test, are relatively inexpensive, and are fast, with results in 1 to 6 hours. Although they have high specificity (83% to 98%), their main drawback is that they are less sensitive (75% to 95%) than the cytotoxicity test. Hence, toxin EIA is now seldom used as a standalone test but is usually combined with a more sensitive assay (such as GDH or NAAT). In addition, some EIA kits only detect toxin A, in which case diarrhea caused by a toxin A+/B− strain of *C. difficile* will have a falsenegative test result. For this reason, assays that can detect both toxin A and toxin B are preferred.

**Two-Step Testing**

Immunoassays also have been used to detect *C. difficile* common antigen (GDH) in stool. The initial latex agglutination assay method lacked diagnostic accuracy and is not recommended. More recent EIAs for fecal GDH have shown high sensitivity (85% to 95%) and specificity (89% to 99%), and are rapid, and are not expensive. These changes have led to the use of EIA for GDH as an initial screening test, with confirmation of positive results using another test such as a EIA or NAAT. If the EIA is negative after a positive GDH, the stool sample is considered indeterminate and the test is arbitrated by a NAAT. If an initial GDH EIA is negative, no additional testing is required (see Fig. 112.6).

**NAAT**

PCR and other NAATs can detect toxinogenic *C. difficile* in clinical isolates. Recent systematic reviews of PCR assays indicate sensitivities and specificities in excess of 90% compared with toxinogenic culture or cytotoxicity assays and superior performance compared with toxin EIA. Two emerging phenomena regarding the widespread use of NAATs for CDI are: (1) introduction of NAATs in place of EIA may lead to an apparent improvement in the incidence of positive test results because of greater sensitivity and (2) there is discussion as to whether NAATs may be “too sensitive” and detect tiny amounts of *C. difficile* genes that are not associated with true colonization or infection. This highlights the importance of interpreting test results in clinical context. Regardless of these issues, the use of NAATs to diagnose CDI has increased greatly.

**Tissue Culture Cytotoxicity Assay**

The tissue culture cytotoxicity assay was the first clinical test to identify *C. difficile* toxins in stool. Toxins A and B inactivate rho proteins, causing a disintegration of the actin cytoskeleton and a characteristic rounding of cells in the tissue culture. Despite its high sensitivity (67% to 100%) and specificity (85% to 100%), the test is currently seldom used because it requires 48 to 72 hours for completion, is expensive, and requires a tissue culture facility.

**C. difficile Culture**

Culture of stool for *C. difficile* is sensitive (89% to 100%) but is not specific for toxin-producing strains of the bacterium. Therefore, cultured isolates must be tested in vitro for toxin production to improve test specificity, but this is costly and time consuming. One advantage of culturing *C. difficile* is that it permits strain typing of individual isolates, and, therefore, it is useful in tracking hospital outbreaks for epidemiologic studies.

**Sigmoidoscopy and Colonoscopy**

Neither sigmoidoscopy nor colonoscopy is required for diagnosis in most patients with *C. difficile* diarrhea. Endoscopic evaluation is helpful, however, when the diagnosis is in doubt or when disease severity demands rapid diagnosis. Sigmoidoscopy may be normal in patients with mild diarrhea or might demonstrate non-specific colitis in moderate cases. The finding of colonic pseudomembranes in a patient with AAD is virtually pathognomonic for *C. difficile* colitis (Fig. 112.7). However, pseudomembranes also may be seen in patients with non-CDI bacterial, viral or parasitic colitis, and also with ischemic colitis. Pseudomembranes appear as yellow, gray, or white plaques 2 to 5mm in diameter, and in some areas they can coalesce to cover large portions of the mucosal surface. Sigmoidoscopy might not be sufficient to identify all patients with pseudomembranous colitis, because 15% to 20% only have pseudomembranes in the more proximal areas of the colon. Other nonspecific endoscopic findings include erythema, edema, friability, small ulcerations, and erosions.

In mild disease, colonic mucosal biopsies may be normal or demonstrate only mild and nonspecific acute inflammatory changes with neutrophil infiltration. In more severe cases, colonic histology shows focal ulceration of the mucosa associated with the eruption of inflammatory cells and necrotic debris that covers the area of ulceration, the so-called summit or volcano lesion (Fig. 112.8).

**Miscellaneous Laboratory Tests**

Many patients with acute *C. difficile* diarrhea develop a polymorphonuclear leukocytosis with a left shift. Occasionally, a leukemoid reaction with an extremely high WBC count of >50,000 or even 100,000 cells/mm³ is seen. A peripheral WBC count of >15,000 cells/mm³ is associated with negative clinical outcomes and a count of >25,000 cells/mm³ is associated with an increased

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**TABLE 112.3 Stool Tests for the Diagnosis of CDI**

<table>
<thead>
<tr>
<th>Test</th>
<th>Target</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue culture cytotoxin</td>
<td>Toxin B (toxin A is 100- to 1000-fold less potent as a cytotoxin)</td>
<td>Traditional gold standard; highly sensitive and specific</td>
<td>Requires tissue culture facility; takes 24-48 hr</td>
</tr>
<tr>
<td>Enzyme immunoassay</td>
<td>Toxin A and/or B</td>
<td>Fast (2-6 hr); easy to perform; specific</td>
<td>Not as sensitive as the cytotoxin or NAATs</td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>GDH</td>
<td>Fast (2-6 hr); easy to perform; sensitive</td>
<td>Not specific; positive results must be confirmed by a more specific assay</td>
</tr>
<tr>
<td>Culture</td>
<td>Toxinogenic and nontoxigenic C. difficile</td>
<td>Sensitive (current gold standard); allows strain typing in epidemics</td>
<td>Requires anaerobic culture; isolates must be tested for toxigenicity; takes 2-5 days</td>
</tr>
<tr>
<td>PCR and other NAATs</td>
<td>Genes specific to toxinogenic C. difficile</td>
<td>Fast (1-4 hr); easy to perform; sensitive</td>
<td>More expensive; requires special equipment; may detect C. difficile genes in the absence of active infection and toxin production</td>
</tr>
</tbody>
</table>

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*Blood test: Toxins A and B are not associated with true colonization or infection. This high-sensitivity and (2) there is discussion as to whether NAATs may be “too sensitive” and detect tiny amounts of *C. difficile* genes that are not associated with true colonization or infection. This highlights the importance of interpreting test results in clinical context. Regardless of these issues, the use of NAATs to diagnose CDI has increased greatly.*

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*In stool specimens, *C. difficile* is negative, no additional testing is required. If an initial GDH EIA is negative after a positive GDH, the stool sample is considered indeterminate and the test is arbitrated by a NAAT. If an initial GDH EIA is negative, no additional testing is required (see Fig. 112.6).*

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mortality risk. Decreased serum albumin and elevated creatinine levels are also markers of severe disease. Patients with protein-losing colopathy and severe hypoalbuminemia can develop peripheral edema, ascites, or anasarca.

Treatment

The first step in the management of CDI is to discontinue any precipitating antibiotics if possible. Concomitant treatment with antimicrobials other than those used to treat CDI is associated with poor outcomes of CDI therapy; in one study, these included a lower and slower initial response to therapy (median time to resolution of diarrhea of 96 vs. 52 hours; \( P < 0.001 \)), higher treatment failure rates after 10 days (16% vs. 7%; \( P < 0.001 \)), and lower rates of sustained response without recurrence (66% vs. 75%; \( P = 0.005 \)).

If all antibiotics are discontinued, diarrhea resolves in approximately 15% to 25% of patients over 2 to 6 weeks without specific anti-\( C. difficile \) therapy. Conservative therapy alone, however, is not appropriate in patients who are severely ill or who have multiple active medical problems, and is seldom recommended in current hospital practice. In patients with active infections elsewhere (e.g., pneumonia, urinary tract infection) and in whom antibiotic therapy must be continued, the antibiotic regimen should be changed, if appropriate, to agents with a relatively low likelihood of exacerbating \( C. difficile \) diarrhea; for example, parenteral aminoglycosides, trimethoprim, or erythromycin (see Table 112.2). Antimotility agents such as diphenoxylate plus atropine (Lomotil), loperamide (Imodium), or narcotics often are avoided because of concern for impaired toxin clearance or precipitation of ileus and toxic dilatation, albeit the evidence supporting these concerns is limited and contradictory.

Many antimicrobial agents show activity against \( C. difficile \) in vitro, and resistance to cephalosporins is so widespread that cefoxitin is added to selective media used to culture \( C. difficile \). Clindamycin resistance is seen in some clinical isolates of \( C. difficile \) and has been associated with nosocomial outbreaks of CDI. There is increasing evidence of fluoroquinolone resistance among nosocomial \( C. difficile \) isolates, and the NAP-1 strain that has caused several outbreaks shows high-level fluoroquinolone resistance. Despite increasing clinical failures with metronidazole, resistance to this drug is rare, and resistance to vancomycin is essentially nonexistent. In one study of 186 clinical isolates of \( C. difficile \), all were sensitive to both metronidazole and vancomycin, with minimum inhibitory concentrations of 0.5 to 4 mg/mL. In another series from Spain, 6% of 415 isolates showed intermediate sensitivity to metronidazole (minimum inhibitory concentration >16 mg/mL), but this partial resistance pattern was not clonal and was not sustained in serial culture. These findings suggest acquired tolerance rather than genetically determined metronidazole resistance.

Many antimicrobial agents, such as ampicillin or amoxicillin, which have in vitro activity against \( C. difficile \), are common causes of \( C. difficile \)-associated diarrhea in clinical practice. These observations illustrate the fact that in vitro sensitivity testing alone is a poor predictor of therapeutic efficacy in this disease. Specific antibiotic therapy to eradicate \( C. difficile \) is required in patients with severe symptoms or in those whose symptoms persist despite discontinuation of antibiotic treatment.

Treatment for an Initial Episode of CDI

The recommended, first-line, antimicrobials for the treatment of CDI are oral vancomycin (125 mg 4 times a day for 10 days) and or oral fidaxomicin (200 mg 2 times daily for 10 days) (see Box 112.2). These 2 agents showed similarly high initial clinical response rates when used to treat CDI in 2 randomized control trials (86% and 88% respectively; \( P = 0.36 \)). Metronidazole appears to be less effective for CDI therapy,
especially in severe disease, and is now recommended for primary CDI therapy only in patients with nonsevere disease if vancomycin and fidaxomicin are not available.

Bacitracin, teicoplanin, nitazoxanide, rifaximin, and fusidic acid also have been used to treat acute infection but have few, if any, advantages over metronidazole, vancomycin, or fidaxomicin. The advantages and disadvantages of specific therapeutic agents are discussed in the sections that follow.

Vancomycin
Vancomycin was introduced for treating CDI in 1978 and now is a recommended first-line treatment for this disorder.\textsuperscript{57,152} The efficacy of vancomycin in treating CDI has been demonstrated in controlled trials.\textsuperscript{141,151-158} Improvement in diarrhea is usually evident within 72 hours of initiating therapy, and complete resolution of symptoms occurs in most patients by the end of a 10-day treatment course.\textsuperscript{57,141,151-158}

The pharmacokinetic properties of vancomycin make it an ideal agent for treating CDI. When given orally, vancomycin is neither absorbed nor metabolized significantly and, as a result, high concentrations are achieved in the colonic lumen. Because oral vancomycin is not absorbed appreciably, systemic side effects are rare. Vancomycin therapy is recommended now for patients with mild, moderate or severe CDI, including patients who fail to respond to metronidazole, are intolerant of metronidazole, are pregnant, or are younger than 10 years of age.\textsuperscript{26,128,150,159,160}

Fekety and coworkers\textsuperscript{161} demonstrated that vancomycin at a dose of 125 mg 4 times a day is as effective as vancomycin 500 mg 4 times a day. The lower dose is recommended for most patients; the higher dose is only recommended for patients with fulminant disease (see later). Vancomycin may be administered by mouth, NG tube, or even by enema.\textsuperscript{122,159} but it should not be given IV to treat CDI because effective colonic luminal concentrations are not obtained with parenteral administration.\textsuperscript{162,163}

Limitations to vancomycin use include concerns regarding the spread of vancomycin-resistant enterococci and the high cost of oral vancomycin capsules.\textsuperscript{160} Generic vancomycin formulated for IV administration is less expensive and can be administered orally with substantial cost savings.

Fidaxomicin
Fidaxomicin is now another recommended first-line agent for treatment of CDI. It is a novel macrolide antibiotic, is active in vitro against clinical isolates of \textit{C. difficile}, has very little systemic absorption and hence few systemic side effects, and achieves high fecal concentrations, making it an attractive therapeutic agent for CDI.\textsuperscript{151,157,164} Furthermore, fidaxomicin shows more limited activity against other members of the intestinal microbiota, suggesting that it may be a more selective therapy against \textit{C. difficile} and lead to fewer post-treatment recurrences.\textsuperscript{151,165}

Clinical trials have compared fidaxomicin (200 mg twice daily) with vancomycin (125 mg 4 times daily) for treatment of CDI.\textsuperscript{151,157} Initial response rates (i.e., resolution of diarrhea at the end of 10 days of treatment) were similar for both agents (88.2% for fidaxomicin \(n = 287\) and 85.8% for vancomycin \(n = 309\) by modified intention-to-treat analysis).\textsuperscript{151} Recurrence rates over the subsequent 4 weeks were lower for fidaxomicin than for vancomycin (15.4% vs. 25.3%; \(P = 0.005\)). A sustained response to therapy (i.e., resolution of diarrhea without recurrence) was more common in the fidaxomicin group (74.6% vs. 64.1%; \(P = 0.006\)). These study findings led to the approval of fidaxomicin for therapy of CDI in many countries, making it the first newly approved therapy for CDI since approval of vancomycin 25 years earlier.

Although fidaxomicin was more effective than vancomycin overall, especially in achieving lower recurrence rates, this benefit was not seen for patients infected by NAP-1 strains. For the 36% of patients with the NAP-1 strain, rates of initial response and recurrence were the same as those with vancomycin; however, for the 64% of patients with other strain types, the recurrence rate was 7.8% with fidaxomicin versus 25.5% for vancomycin (\(P < 0.001\)).

The advantage of fidaxomicin over vancomycin in achieving lower recurrence rates also was demonstrated after combining patients who were treated for a first recurrence of CDI in 2 separate but similar clinical trials.\textsuperscript{166} Second recurrences within 4 weeks of completing therapy developed in 13 of 66 patients treated with fidaxomicin and in 22 of 62 treated with vancomycin (19.7% vs. 35.5%; \(P = 0.045\)). In summary, fidaxomicin is as effective as vancomycin for initial treatment of CDI. It leads to fewer post-treatment recurrences in patients infected with non-NAP-1 strains of \textit{C. difficile}. It also is associated with fewer subsequent recurrences in patients treated for a first recurrence of CDI. Hence, it is now a recommended treatment for either initial or a first recurrence of CDI. The main limitation to its use is its high cost; however, this may be offset, at least partially, by cost savings arising from fewer C. difficile recurrences.\textsuperscript{167,168}

In a recent randomized, controlled, open-label, study, patients with initial or recurrent CDI received extended-pulsed fidaxomicin (300 mg daily on days 1 to 5, then once daily on alternate days on days 7 to 25) or vancomycin (125 mg oral capsules, 4 times daily on days 1 to 10).\textsuperscript{169} The primary endpoint was sustained clinical cure (initial clinical response to therapy without subsequent recurrence) 30 days after end of treatment. One hundred and twenty-four (70%) of 177 patients in the extended-pulsed fidaxomicin achieved sustained clinical cure, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI 1.0–20.7%, \(P = 0.030\); odds ratio 1.62 [95% CI 1.04–2.54]). Hence, extended-pulsed fidaxomicin appears to be an effective treatment for CDI with lower recurrence rates compared with vancomycin.

Metronidazole
Metronidazole (500 mg 3 times daily for 10 days) has been used to treat CDI for several decades but is now considered inferior to vancomycin and fidaxomicin in terms of initial clinical response, especially in those with more severe disease.\textsuperscript{154,158}

Metronidazole was previously a drug of first choice for mild to moderately severe CDI.\textsuperscript{26,130} It is inexpensive and often is effective. Several clinical studies before 2000 indicated that metronidazole therapy resulted in resolution of diarrhea and colitis in more than 95% of patients treated.\textsuperscript{122,141,170} Studies published after 2000, however, report an average failure rate of 19% for metronidazole (range, 7% to 38%); compared with only 4% for vancomycin (range, 3% to 6%).\textsuperscript{25,153,154}

In one small trial, subjects with acute CDI were stratified according to disease severity and then randomized to receive either metronidazole 250 mg or vancomycin 125 mg, each given 4 times per day for 10 days. In mild disease, both treatments yielded similar response rates (90% and 98%; \(P > 0.36\)). In severe disease, however, metronidazole was less efficacious (76% vs. 97%; \(P = 0.02\)).\textsuperscript{153} This finding was later consolidated by the results of a large randomized, controlled trial in which 81% of patients treated with oral vancomycin (\(n = 259\)) showed a favorable initial response to therapy compared with 73% of those treated with metronidazole (\(n = 278\); \(P = 0.02\); OR for clinical
success for vancomycin above metronidazole 1.58 [95% CI 1.04, 2.40; \(P=0.034\)]. In patients with severe CDI, the difference in response to vancomycin (79%) compared with metronidazole (66%) was numerically greater.

Metronidazole, unlike vancomycin, is well absorbed in the upper intestine following oral administration. Fecal concentrations are low or absent in healthy persons or asymptomatic carriers of \(C. difficile\), but higher fecal concentrations are observed in patients with \(C. difficile\) colitis because metronidazole is secreted through the inflamed intestinal mucosa. IV metronidazole (500 mg 3 times per day) may be used in patients who cannot tolerate oral medication because it accumulates to reach bactericidal levels within the inflamed colon.

Oral metronidazole therapy usually is tolerated but can be associated with systemic side effects including nausea, a metallic taste, and a disulfiram-like reaction with alcohol. A peripheral sensory neuropathy may occur with prolonged therapy—especially in older adults; thus, metronidazole should not be administered for prolonged courses. Metronidazole also can potentiate the action of warfarin, resulting in prolongation of the prothrombin time.

Enigmatically, metronidazole has been identified as the anti-biotic agent responsible for causing some cases of \(C. difficile\) diarrhea, demonstrating the importance of reduced colonization resistance in the pathophysiology of \(C. difficile\)-associated diarrhea.

Other Antimicrobial Agents

In randomized therapeutic trials, teicoplanin, 100 mg twice a day for 10 days, was as effective as vancomycin for treating \(C. difficile\) diarrhea. Teicoplanin, however, is relatively expensive and is not available for oral administration in the USA. Nitazoxanide was compared with vancomycin for primary therapy of CDI in a small randomized trial. Response rates after 10 days of therapy were 17 of 22 for nitazoxanide and 20 of 27 for vancomycin (77% vs. 74%; 95% CI for noninferiority, −24% to +28%). There are limited published data on the use of rifaximin, 400 mg 3 times daily for 10 days, as primary therapy for CDI. Bacitracin (25,000 units 4 times daily for 7 to 10 days) is less effective than metronidazole or vancomycin for treating \(C. difficile\) diarrhea, with an overall response rate of only 80% and a relapse rate of 30%. Fusidic acid has been tested in a limited number of patients but appears to be less effective than metronidazole or vancomycin and is associated with a relapse rate of approximately 28%.

Resins, which bind to toxins in the bowel lumen, have been proposed as a possible alternative to antimicrobial therapy for CDI. Clinical studies with 3 different binding resins (colenstipol, cholestyramine, and tolevamer), however, have shown low efficacy compared with standard antibiotic treatment using vancomycin or metronidazole; hence, binding resins are not used as primary therapy for CDI.

Tolevamer is a soluble anionic polymer specifically developed to bind \(C. difficile\) toxins. In a phase 2 human clinical trial, results with tolevamer were similar to those of vancomycin when used as primary treatment for mild or moderately severe infection. In 2 larger phase 3 studies, however, response rates with tolevamer were substantially lower than with either vancomycin or metronidazole. Interestingly, recurrence rates after successful tolevamer treatment were substantially lower than after antibiotic treatment with metronidazole or vancomycin, suggesting its potential use for primary or secondary disease prevention. Tolevamer is not currently in any active trials and is not available for clinical use.

Fulminant (Severe Complicated) CDI

Fulminant CDI, also known as severe complicated CDI, occurs in less than 10% of patients but is associated with a high mortality rate. Diarrhea may be minimal or absent because of ileus, and patients can present with abdominal pain, peritoneal signs, colonic dilatation, marked leukocytosis, and a clinical picture of progressive sepsis with hypotension (possibly requiring the use of a vasopressor), mental status changes, elevated serum lactate, and end-organ failure (e.g., renal, pulmonary). The first step is to discontinue non-\(C. difficile\) antibiotics whenever possible and to start therapy with high-dose oral vancomycin (500 mg 4 times per day), although there are no data to demonstrate that this higher dose is more effective than the standard dose (see Box 112.3). IV metronidazole should be given in addition to oral vancomycin. In the presence of ileus, vancomycin (500 mg every 6 hours) may be administered via NG tube, with intermittent clamping of the tube. Tolevamer may also be administered by enema (500 mg in 100 mL of normal saline).

Fidaxomicin has proven efficacy in treating CDI, but its role in the management of fulminant disease has not yet been examined. In patients not responding to combined treatment with vancomycin and metronidazole, salvage therapy with IV tigecycline (loading dose of 100 mg IV followed by 50 mg 2 times per day) or with pooled human immunoglobulin (400 mg/kg body weight) has been reported; the efficacy of these agents has not been evaluated in controlled clinical trials. Failure of response to vancomycin is not related to acquisition of antibiotic resistance, which has not been documented in clinical isolates of \(C. difficile\), but rather to host factors such as age, immune deficiency, conorbidty, or lack of compliance.

IMT has been used successfully as rescue therapy for patients with severe, complicated CDI that fails to respond to conventional treatment (see later).

Surgery

Surgery is sometimes required in patients with severe colitis not responding to medical therapy, and a surgical consultation should be sought early in patients with severe or fulminant disease. Mortality in severe CDI is usually a result of a marked systemic inflammatory response leading to organ failure. Hence, colon perforation or toxic megacolon are not the sole indicators of a need for surgical intervention. In one study, colectomy appeared to be more beneficial in patients who were not immunosuppressed, were 65 years of age or older, had a leukocytosis of ≥220,000 cells/mm³, or a lactate between 2.2 and 4.9 mmol/L. The standard operation has been a subtotal colectomy with temporary ileostomy, but surgical intervention in this setting is associated with a high perioperative mortality rate. Grundfest-Broniatowski and associates reported an overall mortality rate of 42% in a series of patients who underwent surgery for fulminant, severe CDI. One study reported a different surgical approach whereby a loop ileostomy was fashioned at laparoscopy, and intraoperative colonic lavage was then performed with 8 L of warmed polyethylene glycol colon preparation solution. Postoperatively, vancomycin solution (500 mg in 500 mL of lactated Ringers) was administered through the ileostomy into the colon every 8 hours for 10 days. Of 42 patients with severe complicated CDI treated with this approach, only 7% required colectomy, and the mortality rate was 19% (compared with 50% in historic controls who underwent colectomy; OR, 0.24; \(P=0.006\)). This novel approach may carry several substantial advantages and clearly warrants further study.

Recurrent CDI

One of the most difficult clinical problems in treating patients with CDI is the high incidence of recurrences. Approximately 25% of patients successfully treated with vancomycin or metronidazole suffer a recurrence after completing their initial antibiotic therapy.
Part X Small and Large Intestine

recurrence rates are higher (~35%) in those treated for a first recurrence and may exceed 50% in those treated for a second or subsequent recurrence.

The clinical features of recurrence are similar to the initial episode, with watery diarrhea, cramping abdominal pain, or fever occurring typically 2 to 21 days after discontinuing therapy. Late recurrences are less common but can occur more than 2 months after stopping antibiotic treatment for CDI. The diagnosis of recurrent CDI is best confirmed by stool toxin assay when- ever possible or, in rare instances, by colonoscopy and biopsy. In patients with typical symptoms of recurrence, therapy can be reinstituted while awaiting stool assay results. Prompt therapy is especially important in patients whose initial attack of \textit{C. difficile} diarrhea was severe because they are more likely to suffer from severe recurrent disease, possibly caused by their inadequate immune response to \textit{C. difficile} toxins.\textsuperscript{88,201}

Some patients with persistent symptoms after successful therapy of CDI develop diarrhea as a result of postinfection IBS.\textsuperscript{204} Frequent watery diarrhea and cramping lower abdominal pain may be partially responsive to antibiotic therapy. Patients with post-\textit{C. difficile} IBS have normal colonoscopy and biopsy, and their stools are usually negative on \textit{C. difficile} testing. Other diarrheal conditions that require differentiation from recurrent CDI include IBD, microscopic colitis, celiac disease, and food (e.g., lactose, fructose) intolerance.

Bacteriologic typing studies demonstrate that symptomatic recurrence can result from relapse of infection with the same strain that caused the initial episode or a new infection with a different strain of \textit{C. difficile}.\textsuperscript{205,206} Resistance to metronidazole or to vancomycin is seldom, if ever, an important factor in recurrence. In some patients, \textit{C. difficile} can be identified in the stools during-successful vancomycin therapy, and these patients may be more

\textbf{Box 112.3 Treatment of \textit{C. difficile} Infection}

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment\textsuperscript{a}</th>
<th>Strength of Recommendation/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>Leukocytosis with a white blood cell count of (&lt;15,000 \text{ cells/mL}) and a serum creatinine level (&lt;1.5 \text{ mg/dL})</td>
<td>VAN 125 mg given 4 times daily for 10 days, or FDX 200 mg given twice daily for 10 days</td>
<td>Strong/high</td>
</tr>
<tr>
<td>Initial episode, severe\textsuperscript{1}</td>
<td>Leukocytosis with a white blood cell count of (&gt;15,000 \text{ cells/mL}) or a serum creatinine level (&gt;1.5 \text{ mg/dL})</td>
<td>VAN 125 mg 4 times per day by mouth for 10 days, or FDX 200 mg given twice daily for 10 days</td>
<td>Strong/high</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>VAN 500 mg 4 times per day by mouth or by NG tube. If ileus is present, consider adding rectal instillation of VAN. IV administered metronidazole (500 mg every 8 hr) should be administered together with oral or rectal VAN, particularly if ileus is present.</td>
<td>Strong/moderate</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, or Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10-14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2-8 wk), or FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode</td>
<td>Weak/moderate</td>
</tr>
<tr>
<td>Second or subsequent recurrence</td>
<td>...</td>
<td>VAN in a tapered and pulsed regimen, or VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, or FDX 200 mg given twice daily for 10 days, or IMT\textsuperscript{1}</td>
<td>Weak/low</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

\textsuperscript{1}The criteria proposed for defining severe or fulminant CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

\textsuperscript{1}The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering IMT. FDX, Fidaxomicin; VAN, vancomycin.

likely to relapse than those in whom eradication of the pathogen occurs during therapy; however, \textit{C. difficile} can also be present in stool during and after successful antibiotic treatment in patients who do not relapse.123

Culture positivity during symptomatic improvement might reflect the persistence of antibiotic-resistant spores. In one study, 18 of 22 patients with recurrence were noted to have colonic diverticula, leading to the speculation that spores might survive in diverticula where they escape the normal cleansing action of diarrhea and might not be exposed to the high luminal concentration of antibiotics; however, reinfection by bacterial spores through the usual fecal-oral route is the likely mechanism of recurrence.205,206 One study compared 128 patients with CDI who had diverticulosis to 137 patients with CDI who did not have diverticulitis and found no significant differences between the 2 groups in terms of risk for relapse or recurrence except, perhaps, for the small group of patients with diverticulitis of the ascending colon in whom the risk of relapse was increased.208

**Conservative Therapy**

In a report of 20 patients with clindamycin-associated pseudomembranous colitis, published before the discovery of vancomycin as effective therapy, all patients eventually recovered when clindamycin was stopped.209 An important advantage to this form of management is that recurrence of diarrhea or colitis does not occur, probably because stopping all antimicrobial agents allows restoration of the colonic microbiota, which provides colonization resistance against \textit{C. difficile}. Thus, some patients with mild symptoms of recurrence can be managed conservatively without specific antibiotic treatment, thereby avoiding subsequent recurrences. This approach may not be appropriate for older adults or infirm patients and is not advised for those with moderate or severe symptoms.

**Standard Therapy With Metronidazole, Vancomycin, or Fidaxomicin**

Patients with a first recurrence may be treated with a standard 10-day course of vancomycin or fidaxomicin (especially if metronidazole was used to treat the initial CDI episode) (see Box 112.3).210 As noted earlier, fidaxomicin treatment of an initial episode of CDI is associated with fewer recurrences compared with vancomycin (15.4% vs. 25.3%; 39% reduction; \( P = 0.005 \)).113,116 The benefit of fidaxomicin over vancomycin in reducing subsequent recurrences is also evident in patients with recurrent CDI.113,116,166 In one study of patients treated for a first recurrence, fidaxomicin 200 mg twice daily for 10 days led to a subsequent recurrence rate of 19.7% compared with 35.5% for vancomycin 125 mg 4 times daily for 10 days (45% reduction; \( P = 0.045 \)).166

**Prolonged Antibiotic Regimens for First or Subsequent Episodes of Recurrent CDI**

Tedesco and colleagues207 treated 22 patients who had multiple recurrences of \textit{C. difficile} colitis with tapering doses of vancomycin for a 3-week period, followed by every-other-day therapy for one week and every-third-day therapy for an additional week. All patients responded symptomatically and remained well during a mean follow-up period of 6 months.

Although data from randomized, controlled trials are not available, one subsequent study that examined various physician-selected antibiotic regimens to treat recurrent CDI found that regimens incorporating prolonged or pulsed-dose oral vancomycin were the most effective.210 Overall, 73 of 163 patients (45%) treated for recurrent CDI had a subsequent recurrence. Of all the regimens used, only those that incorporated prolonged-dose vancomycin (9 of 29 recurred [31%]; \( P = 0.01 \)) or pulsed-dose vancomycin (1 of 7 recurred [14%]; \( P = 0.02 \)) showed significantly lower recurrence rates. The mechanism whereby this treatment approach is effective is unknown and might simply reflect prolongation of therapy. A commonly used regimen of tapered and pulsed dose oral vancomycin is presented in Box 112.3.

Toxin production by \textit{C. difficile} does not usually occur during the early exponential growth phase of the bacterium, but rather in the subsequent stationary phase; thus, after active \textit{C. difficile} toxin-induced diarrhea and colitis have been controlled by treatment with vancomycin, a period of 24 to 72 hours is required for the bacteria to reinitiate production and release of toxin. Thus, pulsed dosing might prevent toxin production and release, while also facilitating restoration of the normal colonic microbiota and, hence, \textit{C. difficile} colonization resistance.

**Sequential Therapy With Vancomycin Followed by Rifaximin**

Rifaximin is an orally administered antibiotic with minimal systemic absorption and activity against most \textit{C. difficile} isolates.213,214 In a randomized controlled trial, patients with CDI were treated with rifaximin 400 mg 3 times daily or placebo for 20 days after completing a 10- to 14 day standard course of treatment with metronidazole or vancomycin.215 CDI recurrence developed in 11 of 35 (31%) patients given placebo and 5 of 33 (15%) patients given rifaximin (\( P = 0.11 \)). Although the findings from this small study did not reach statistical significance, the “rifaximin chaser” regimen has been included as a management option for recurrent CDI in recent guidelines.215

**IMT**

IMT first was described in the English language as an effective treatment for fulminant, antibiotic-associated, pseudomembranous colitis in 1958, 20 years before the etiologic role of toxigenic CDI was identified.216 This treatment is based on the recognition that alteration of the bacterial flora of the colon by antibiotics is the major predisposing cause of CDI, and that restoration of the normal microbiota can eliminate the pathogen. Patients with recurrent CDI have been shown to have a decreased phylogenetic richness of their intestinal microbiome with a reduction in the Firmicutes and Bacteroidetes phyla not seen in patients with just one episode of CDI.217 In recent years, IMT has been used mainly to prevent further episodes of CDI in patients in whom treatment for multiple recurrences has failed.31 Typically, fresh feces are obtained from a screened donor, processed, and then administered via NG or nasoenteric tube, by enema, or during colonoscopy; colonoscopy is the route most frequently used today. The overall reported efficacy in uncontrolled studies is high: 81% for the gastric or small intestinal routes and 92% for the rectal or colonic routes.217 In a randomized controlled trial from Europe, nasoduodenal infusion of donor feces was successful in preventing further episodes of recurrent CDI in 81% of patients compared with 31% who received vancomycin therapy (\( P < 0.001 \)) and 23% who received vancomycin with bowel lavage (\( P < 0.001 \)).216 These results (81% efficacy) agree closely with the findings of a systematic review of uncontrolled case series in which gastric or small intestinal infusions were employed. A randomized double-blinded clinical trial from the USA demonstrated that donor IMT via colonoscopy was more effective than autologous IMT for patients with recurrent CDI (90% vs. 62.5%).31 Fresh or freeze-thawed stool has been shown to have similar success for recurrent CDI. Patients with severe and complicated or fulminant CDI also have been shown to benefit from IMT. Studies have detailed a mortality benefit when these patients receive multiple IMT infusions while continuing vancomycin; the number of treatments in this patient population is guided by the presence of severe colitis or pseudomembranes upon repeat colonoscopies. A randomized controlled trial of 56 patients that compared the efficacy of 2 IMT-based protocols (single IMT versus multiple IMTs) in patients with severe CDI refractory to antibiotics showed a 100% cure rate in the multiple IMT group compared with a 75% cure rate in the group that received a single IMT; no serious adverse events were
IMT-based therapies may be considered in refractory severe cases if there is lack of improvement in 3 to 5 days. On these data, there is increasing interest in IMT for the prevention and treatment of CDI. Steps are being taken to make this treatment approach more acceptable and more accessible to patients and their physicians through stool banking to provide already processed treatment units from prescreened donors; defined bacterial culture mixtures also are being developed to replace human feces as the source material. The FDA suggests that IMT be used as an investigational therapy for CDI under enforcement discretion of their guidance, but not for other diseases for which an investigational new drug application is required. As of March 2016, the FDA has provided a draft guidance for IMT, which suggests that a stool donor and stool are qualified by screening and testing performed under the direction of a health care provider for the purpose of providing the IMT product for treatment of a patient with CDI. The screening methodology is not defined by the FDA but there is a general consensus amongst providers to exclude donors who have any communicable disease or diseases possibly related to or associated with an altered microbiome such as metabolic diseases, neuropsychiatric illnesses, IBD, immunocompromise, etc. Donors qualify by a thorough medical history and a full panel of blood, stool and urine tests. The draft guidance also suggests that adequate informed consent be obtained and include a statement that the use of IMT to treat C. difficile is investigational as well as a discussion of its risks and benefits. A final guidance statement regarding FDA regulation of IMT and stool banks is awaited. A commercial not-for-profit stool bank model “Openbiome” has been in operation in the USA with a rigorous donor screening program, along with a large-scale storage and preparation facility for stool with a distribution network all over the USA, making stool widely available to providers; several thousand IMT units are shipped every year. Along with a frozen form of stool for endoscopic delivery, Openbiome also has made oral IMT delivery capsules available and in one study, have shown overall relative cure rates at week 8 for gastric-release and colonic-release capsules of 75% (15 of 20) and 80.6% (25 of 31) respectively; both formulations were safe with no serious adverse events. The colonic-release capsule was deemed superior at increasing intestinal microbial diversity. Standardized capsule-based and enema-based therapies for products derived from human stool are being developed and are in clinical trials for prevention of future recurrent CDI. A capsule-based therapy (SER-109) derived from donor stool treated with ethanol to remove vegetative forms, and stored as frozen capsules, has shown promise in a phase 1 study with unpublished results from a blinded-phase II study showing lack of efficacy, a large phase 3 placebo-controlled study is underway. Similarly, an enema-based product (RBX-2660), again derived from human stool and delivered via an enema without bowel preparation, has shown positive results in a phase 1 open labeled study and a phase 2 placebo-controlled blinded study, a large phase 3 placebo-controlled study is underway.

**Immunization Against C. difficile Toxins**

As described earlier, there is considerable evidence that some persons have protective immunity against CDI and that protection is associated with higher antibody concentrations in serum, intestinal secretions, or both. Leung and coworkers reported on 6 children with multiple relapses of CDI who had low concentrations of serum IgG antibody to toxin A. Five of these children were treated with IV normal immune globulin at a dose of 400 mg/kg, which contained high titer of IgG antitoxin A and antitoxin B. Symptoms resolved following treatment. Similar results have been reported by other investigators, but there are no reported controlled trials of normal immune globulin for treatment or prevention of CDI.  

**Bezlotoxumab: Antitoxin B IgG Human Monoclonal Antibody**

In a randomized controlled trial, human antitoxin A (Actoxumab) and antitoxin B (Bezloxumab) IgG monoclonal antibodies were administered IV to patients receiving antibiotic therapy for acute CDI. As expected, recurrent infection occurred in 25% of the placebo group following completion of anti-C. difficile antibiotic treatment. Conversely, only 7% of those who received the antitoxin antibodies suffered a recurrence (P = 0.001), clearly demonstrating the clinical potential for passive immunotherapy in CDI. In a subsequent phase 3 double-blind, randomized, placebo-controlled, clinical trials examined CDI recurrence following IV infusion of actoxumab, bezloxumab, both antitoxin monoclonal antibodies or placebo to patients with primary or recurrent CDI. The primary endpoint was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion. Bezloxumab was not effective in reducing CDI recurrence. Bezloxumab neutralizes C. difficile toxin B by binding to its putative receptor-binding domain. In both trials, bezloxumab (10 mg/kg), infused during standard of care antibiotic therapy for CDI, was associated with fewer CDI recurrences during the subsequent 12 weeks (16.5% compared with 26.6% for placebo). The rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64% for bezloxumab and 54% for placebo. Bezloxumab had a safety profile similar to that of placebo.

Patients with at least one known risk factor for recurrent CDI (prior CDI, age ≥65 years, infection with 027/078/244 strains, compromised immunity, or severe CDI) showed higher recurrence rates with placebo and a greater reduction with bezloxumab (37.2% to 21.2%; −15.9; −21.6, −10.2). Conversely, those lacking all of these risk factors did not show substantial benefit and the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 56% for bezloxumab and 45% for placebo. Bezloxumab has been approved for reduction of recurrent CDI episodes when infused during standard-of-care antibiotic therapy for CDI, in patients at high risk for recurrence.

**C. difficile Vaccines**

Several C. difficile toxin vaccines have been produced. The most studied to date in clinical trials contains chemically inactivated toxoids A and B. In early clinical trials, this vaccine was immunogenic and in a small case series, vaccination was associated with resolution of recurrent C. difficile diarrhea in 3 subjects. Subsequent studies identified a vaccination regimen that effectively induced antitoxin antibody responses. A Phase 3 vaccine trial for CDI prevention was initiated but was closed in 2017 after an interim review of the study data indicated that the study was unlikely to reach its objectives. A second C. difficile vaccine using genetically and chemically inactivated toxoids A and B is in late-stage clinical development.

**Probiotic Therapy**

In contrast to treatment with antimicrobial agents that further delay recolonization by normal colonic bacteria, probiotic agents are an attractive addition to antibiotic therapy for recurrent CDI because restoration of colonization resistance can lead to permanent eradication of C. difficile from the colon. In an open-label study, Lactobacillus strain GG was reported to be effective in preventing diarrhea in patients with recurrent C. difficile colitis. Another placebo-controlled study of hospital patients receiving antibiotics used a probiotic drink mixture containing L. casei, L. bulgaricus, and Streptococcus thermophilus (DanActive) and found that simple AAD was reduced from 34% to 12% (placebo vs. active; P = 0.007), and CDI was reduced from 17% to 0% (placebo vs. active; P = 0.001). Protection against AAD and against CDI was also reported with a probiotic mixture containing L. acidophilus and L. casei. The reproducibility of these positive results using Lactobacillus-containing probiotic mixtures needs to be confirmed in additional, multicenter controlled trials.
The yeast *S. boulardii* is widely used as a probiotic agent in continental Europe and is available in the USA without prescription. In a double-blind controlled clinical trial, coadministration of oral capsules containing viable *S. boulardii* with antibiotics significantly reduced the incidence of AAD in hospitalized patients (from 22% on placebo to 9.5% in the *S. boulardii* group; \( P = 0.04 \)). In that study, however, few patients had *C. difficile*–associated diarrhea. A second randomized placebo-controlled trial examined the efficacy of *S. boulardii* in combination with either metronidazole or vancomycin in patients with *C. difficile* diarrhea. Diarrhea recurrence rates were similar in subjects treated during their first episode of *C. difficile* diarrhea (19% in the *S. boulardii* group vs. 24% in the placebo group; \( P = 0.86 \)). In contrast, patients with a history of recurrent *C. difficile* diarrhea who received *S. boulardii* had fewer recurrences than the placebo group (35% and 65%, respectively; \( P = 0.04 \)). In a subsequent study, however, *S. boulardii* had no overall effect on recurrence rates (44% vs. 47% with placebo). *S. boulardii* should not be administered to immunocompromised patients because of the risk of fungemia.

Another oral live bacterial therapy used for prevention of recurrent CDI is a nontoxinogenic strain of *C. difficile* (NTCD). NTCD strain M3 was well tolerated in an initial safety study. In a subsequent Phase 2 randomized, double-blind clinical trial, patients received NTCD strain M3 or placebo following standard treatment for CDI with metronidazole or vancomycin. The CDI recurrence rate in the NTCD-treated group was 11% compared with 30% for placebo (OR 0.28, 95% CI 0.11–0.69; \( P = 0.006 \)). Despite these promising safety and efficacy findings, NTCD strain M3 is not in any active clinical trials at the time of writing.

### Overall Approach to Recurrent CDI

The management of a first episode of recurrent *C. difficile*–associated diarrhea does not differ greatly from treatment of an initial episode (see Box 112.3). Stool samples should be obtained to reconfirm infection with toxigenic *C. difficile*. Patients with mild symptoms of recurrence may be managed conservatively without additional antibiotic treatment, just like patients with a primary episode. If symptoms persist or are severe, a standard course of vancomycin, or fidaxomicin should be administered. If a second recurrence occurs, other treatment approaches should be considered.

Fidaxomicin has the unique advantage of proven lower recurrence rates in randomized controlled trials, both in primary therapy and in treatment of a first recurrence. Tapering and pulsed antibiotic regimens are well tolerated and often successful. IMT has proven efficacy in patients with multiple previous recurrences of CDI and is quickly becoming a routine part of management. A wide range of other approaches have been described, some of which are summarized in Box 112.3.

In some instances, multiple recurrences occur, and a variety of different regimens must be used before the organism is finally eradicated. In other cases, recurrences persist despite several different treatment approaches; in such cases, extremely prolonged therapy with oral vancomycin (125 mg once or twice daily) is a pragmatic and effective means to prevent further recurrences. This approach is indicated in high-risk patients for whom other measures, including multiple antibiotic regimens, have failed, and especially in those with severe underlying disease, a high likelihood of needing additional courses of antibiotic treatment, and where life expectancy is short.