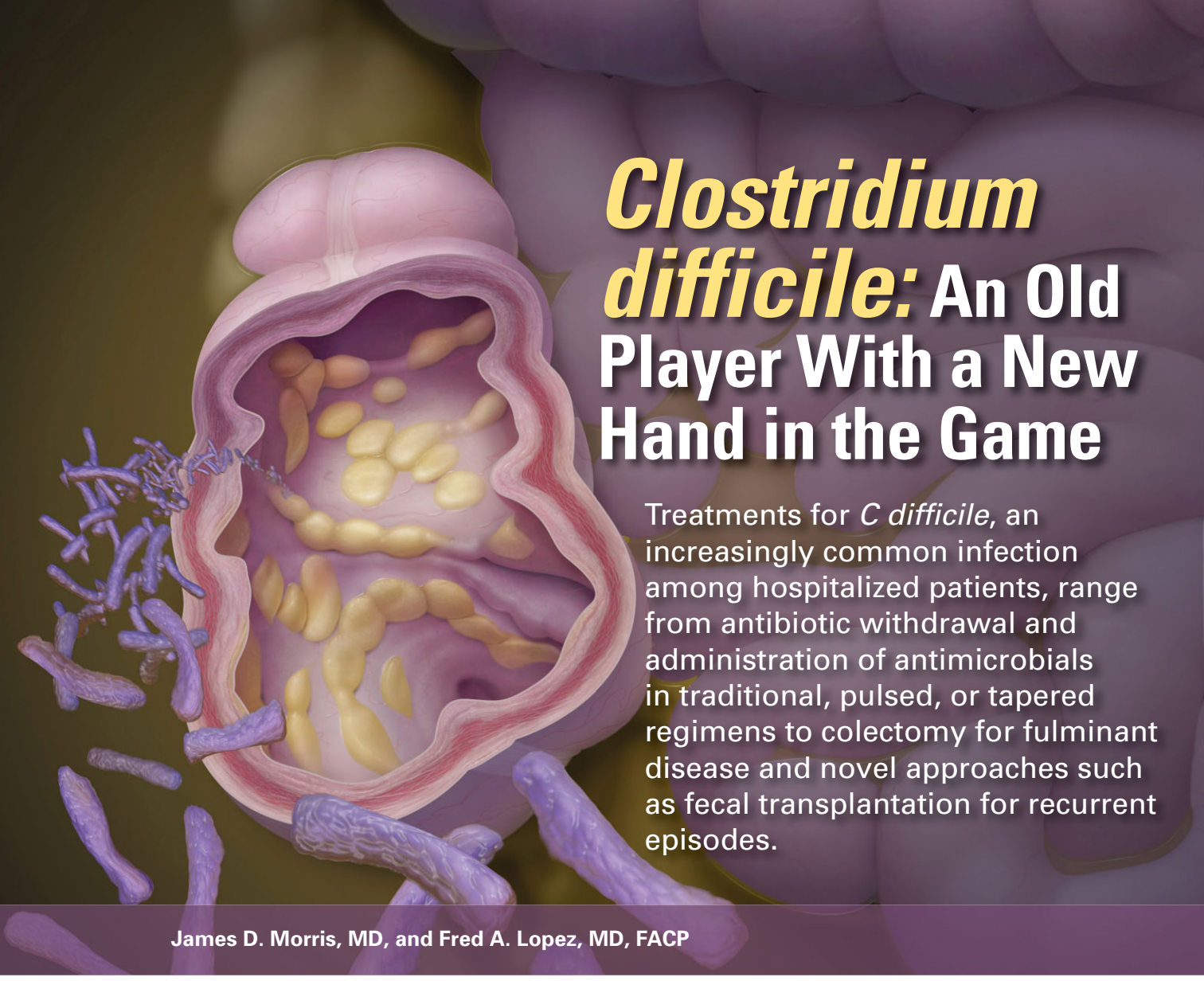

# *Clostridium difficile:* An Old Player With a New Hand in the Game

Treatments for *C difficile*, an increasingly common infection among hospitalized patients, range from antibiotic withdrawal and administration of antimicrobials in traditional, pulsed, or tapered regimens to colectomy for fulminant disease and novel approaches such as fecal transplantation for recurrent episodes.

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*Clostridium difficile* has emerged as a major nosocomial pathogen for patients undergoing antibiotic therapy and receiving inpatient hospital or institutionalized care. At particular risk are those in the elderly population. Since 2000, the number of cases of *C difficile*, as well as the disease-associated financial burden, has grown enormously. Preventing, recognizing, and combating this disease process is paramount for all health care organizations, particularly in the ED, as it is the gateway to hospital care.[1]

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*C difficile* infection (CDI) is the recommended terminology for *C difficile*–induced disease, which encompasses pseudomembranous colitis or antibiotic-associated diarrhea. Recent literature indicates that CDI costs the US health care system more than $1.1 billion each year, with approximately 15% to 20% of hospitalized patients becoming infected.[2,3] The overall incidence of the disease has been increasing at a substantial rate, as documented by multiple epidemiologic studies in the United Kingdom, Canada, and the United States. A particularly virulent strain has emerged in Quebec and in the United States (specifically Georgia, Illinois, Maine, New Jersey, Oregon, and Pennsylvania), resulting in a significant increase in mortality.[4,5]

*C difficile* virulent strain NAP-1/027, which appears to have increased toxin A/B production, fluoroquinolone resistance, and production of binary toxin, has been associated with severe infection and

high mortality. Fluoroquinolone use has greatly expanded in recent years, due to the agent's broad spectrum of activity and the ease of once- or twice-daily administration. Use of any class of antibiotic with antibacterial activity constitutes a theoretical risk factor for CDI, although, historically, clindamycin, aminopenicillins, and cephalosporins have had the strongest associations.[6,7]

*C difficile* is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus transmitted among humans via the fecal-oral route.[8] The bacteria are typically transmitted in hospitals. Alcohol-based rubs/gels have little or no activity against the spores of *C difficile*. Additional risk factors for *C difficile* colonization include older age (nursing home or rehabilitation center admission), antibiotic use, bowel surgery,[9] use of a feeding tube, and chemotherapy (rarely methotrexate). Children up to age 18 months may be carriers of the organism (up to 60% to 70% are colonized); however, colitis rarely develops.[2] Colonization usually disappears within a few months and is thought to result from a lack of receptors for *C difficile*–associated toxins.[10] Inanimate objects in a patient's room may harbor the acid- and antibiotic-resistant spores for weeks to months, thus necessitating comprehensive cleansing of contaminated spaces in health care facilities. Acid suppression has an unclear role in CDI, with conflicting data supporting or refuting its association with infections. Inflammatory bowel disease also appears to be a risk factor for superimposed infection, and its presence together with active inflammation may also make it difficult to detect CDI on endoscopy.[11] To control CDI, the following precautions are paramount: contact isolation (with patients in a single room and no sharing of bathrooms), wearing gloves, washing hands with soap and water, terminal room cleaning with 1:10 household bleach, avoidance of use of rectal thermometers, decreased length of hospitalization, decreased antibiotic usage, and early isolation of suspected infected patients.[10,12]

## CLINICAL PRESENTATION

Presentation varies from mild symptoms to severe toxic colitis.[2] Diarrhea can range from a "nuisance" to more than 20 watery bowel movements daily. Crampy lower quadrant abdominal pain may be present in addition to variable degrees of fever. Leukocytosis (particularly >20,000 leukocytes/mm$^3$) may also be present and, when it appears with renal dysfunction (elevated creatinine), may lead to a higher risk for severe colitis and increased mortality (Table 1).[2] CDI is a protein-losing enteropathy that can result in low serum albumin levels. In more severe disease, pseudomembranous colitis may develop with characteristic white plaques scattered throughout the colon and sometimes even the small intestine. In the worst cases, a fulminant colitis may develop. Perforation is rare. Fecal leukocytes are commonly present but provide only a general clue to an infectious or inflammatory etiology.[13]

**TABLE 1. Risk Factors for Severe *Clostridium difficile* Infection**

| | |
|---|---|
| Severe diarrhea | Ileus |
| High fever, >38.9˚ C | Age >60 years |
| High leukocytosis (>20,000 leukocytes/mm$^3$) | Albumin <2.5 mg/dL |
| Renal failure | Pseudomembranous colitis |

Data extracted from Leffler and LaMont.[2]

## CLINICAL DIAGNOSIS

CDI can generally be diagnosed using both clinical and laboratory information. The use of radiologic imaging (CT) or endoscopic evaluation is usually not required. Stool cytotoxicity assays initially were introduced for the detection of CDI; however, they have largely been replaced by enzyme immunoassays. Detection of both toxins A and B is suggested, as a small number of strains will produce only cytotoxin B.[14] These newer tests may lack the sensitivity/specificity of earlier cytotoxicity assays. In the presence of strong clinical suspicions in acutely ill patients, therapy for CDI should be initiated early, even if immunoassays are negative. Stool culture using special media may also be performed, but this technique is limited to only a few specialized centers and is most useful in epidemiologic studies. As this infection becomes more endemic, suspected CDI should prompt only one immunoassay, as the majority of the first samples

**>>FAST TRACK<<**

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will be positive. The diagnostic yield of repeated enzyme immunoassays is low and leads to unnecessary expense.[15] Radiologic examination with plain films or cross-sectional imaging (CT) may provide supportive evidence of infection and prove valuable in patients presenting with fulminant colitis. Severe disease is suggested on CT by colonic wall-thickening, colonic dilation, and ascites.[16]

## TREATMENT

### General Issues

Not all patients with positive immunoassay results and clinical evidence of symptoms require therapy. Withdrawal of an antimicrobial agent may lead to eradication of CDI in a quarter of cases but should be limited to the mildest cases. However, most patients present with acute disease and require antibiotic treatment. Toxin-binding resins and probiotics have not definitively been proven as effective treatment. Cholestyramine binds vancomycin in the gastrointestinal (GI) tract, ie, decreasing the effectiveness of vancomycin and requiring a 2- to 3-hour alternating period between drug administrations. In addition, drugs that impair GI motility, including narcotics, should be avoided.[2]

### Antibiotic Issues

Antibiotics are usually curative, although severe cases may necessitate a colectomy (Table 2).[1,2,16,17] Initial choice of antibiotic therapy continues to generate much discussion. Oral metronidazole (500 mg 3 times a day or 250 mg 4 times a day for 10 to 14 days) has historically been the initial choice for treatment of CDI[18]; however, oral vancomycin (125 mg 4 times a day for 10 to 14 days) is the only agent approved by the FDA for the treatment of this condition. Metronidazole's lower cost provides an argument for its initial use in mild disease, but recent studies suggest that the drug is less efficacious than vancomycin. Use of vancomycin may promote the development of vancomycin-resistant enterococci, but resistance has also been noted with metronidazole. Studies supporting initial therapy with vancomycin are emerging. In one series, the difference in response rates between vancomycin and metronidazole was not significant in patients with mild infection ($P$=.36) but achieved significance in favor of vancomycin for those with severe infection ($P$=.02).[19]

**>>FAST TRACK<<**

**For the first recurrence of CDI, the patient should be re-treated with the original drug (ie, oral vancomycin or oral metronidazole).**

For the first recurrence of CDI, the patient should be re-treated with the original drug (ie, oral vancomycin or oral metronidazole).[1] Oral vancomycin has minimal side effects, although patients may experience gastric upset and nausea. Side effects associated with parenteral administration, including ototoxicity, nephrotoxicity, and red man syndrome, have not been observed with oral dosing. Metronidazole's side effects include headache, nausea, metallic taste, and a disulfiram-like effect when alcohol is ingested. Prolonged exposure to metronidazole (>1 month) may cause a potentially irreversible neuropathy.[2]

### Fulminant Disease

In those patients with severe disease represented by a leukemoid reaction, renal dysfunction, ileus, inability to tolerate oral intake, and/or high fever, ICU admission should be considered. Diarrhea may be absent in some of these cases, thereby complicating the ability to make a diagnosis. Early surgical evaluation should be considered in patients with fulminant disease. Functionality of the gut should be assessed within 24 to 48 hours of presentation, and clinical improvement should be expected in 3 to 5 days.[16]

The functionality of the GI tract is an important consideration when determining whether oral antibacterial agents can be administered to a patient. In patients with a functional GI tract who are unable to tolerate oral intake, a nasogastric tube may be used for delivery of metronidazole or vancomycin. If ileus is present, vancomycin administered by enema may be considered (0.5 to 1.0 g in 100 to 200 mL normal saline given as a retention enema with the rectal tube clamped for 60 minutes every 4 to 12 hours). Adjunctive IV metronidazole may also be given; however, less than 15% of the IV dose is excreted via the fecal route; thus, this treatment may have limited efficacy in the presence of ileus. Surgical treatment is indicated in patients with signs of organ failure, shock, vasopressor dependence for hemodynamic stability, worsening signs on CT, peritonitis, bowel perforation, clinical worsening, or lack of response within 72 hours (or sooner if morbidity is more severe). Delays in diagnosis and treatment increase mortality. Currently, total abdominal colectomy with end ileostomy is the operative procedure

## TABLE 2. Antimicrobial Therapy Strategy Choices for *Clostridium difficile* Infection

**All Cases:** Stop or change antibiotics, use supportive therapy, enforce infection control precautions, isolate patient

| Mild Disease | Severe Disease |
|---|---|
| Metronidazole 500 mg orally 3 times daily for 10–14 days with daily assessments | *For patients with a functional GI tract*<br>Vancomycin 125 mg oral/nasogastric tube 4 times daily for 10–14 days with daily assessment ± metronidazole 500 mg IV every 6 hours for 10 days<br>*For patients with ileus*<br>Vancomycin 500 mg in 100–200 mL normal saline as retention enema clamped for 60 minutes every 4–12 hours for up to 10 days ± metronidazole 500 mg IV every 6 hours for 10 days<br>Early surgical evaluation for colectomy<br>Infectious disease consultation<br>Possible gastroenterology consultation for colonoscopy |
| *No response or worsening of symptoms in 7 days*<br>Vancomycin 125 mg orally 4 times daily for 10–14 days<br>Infectious disease consultation<br>Gastroenterology consultation<br>Possible surgical referral if severe symptoms (leukocytosis, renal dysfunction, ileus, hypotension) | *No response or worsening of symptoms in 72 hours*<br>Daily assessment<br>Colectomy<br>If colectomy not warranted, vancomycin 500 mg orally every 6 hours up to 10–14 days<br>Consider IVIG, 400 mg/kg |

GI=gastrointestinal; IV=intravenous; IVIG = intravenous immunoglobulin
Data extracted from Kelly and LaMont[1]; Leffler and LaMont[2]; Jaber et al[16]; Gerding et al.[17]

of choice for fulminant CDI. The reported mortality rate in surgical treatment of CDI ranges from 30% to 80%.[16]

### Recurrent Disease

Approximately 20% of patients will develop a recurrence of symptomatic CDI.[1,2,16,17] Older patients and those with a history of CDI recurrence are at increased risk. Most recurrences occur shortly after the end of therapy (ie, 7 to 14 days). Repeat exposure to *C difficile* spores or lack of eradication of the bacteria can lead to these repeat episodes. Host immunity also contributes to recurrent disease. Development of immunoglobulin G antitoxin A at high levels appears to be protective for recurrent disease, while low levels may confer risk for recurrent disease.[1] Failure to achieve eradication with the same antibiotic following the second course of treatment should prompt reevaluation of the patient. Stool immunoassay studies for *C difficile* toxins should be repeated, as postinfectious irritable bowel syndrome and other bacterial infections may have similar presentations. Antimicrobial resistance to vancomycin has not been reported, and resistance to metronidazole is rare.[17]

In recurrent CDI, regimens with tapering or pulsed vancomycin administration resulted in fewer recurrences, with recurrence rates of 31% ($P$=.01) for tapering and 14.3% ($P$=.02) for pulsed administration when compared to standard metronidazole or vancomycin treatments.[1] Table 3 shows treatment strategies

## TABLE 3. Treatment Strategies for refractory *Clostridium difficile* Infections

| Initial Recurrence | |
|---|---|
| Repeat regimen of metronidazole 500 mg orally 3 times daily for 10–14 days | |
| **OR** | |
| Vancomycin 125 mg orally 4 times a day for 10–14 days (severe disease or intolerant of metronidazole) | |
| **Second Recurrence** | |
| *Taper regimen*—Vancomycin 125 mg orally 4 times daily for 7 days, 125 mg 2 times daily for 7 days, 125 mg once daily for 7 days, 125 mg once every 2 days for 8 days, and 125 mg once every 3 days for 15 days | *Pulse regimen*—Vancomycin 125 mg orally 4 4 times daily for 14 days, then 125 mg 3 times a week for an additional 4 weeks |
| **Third Recurrence** | |
| Vancomycin 125 mg orally 4 times daily for 14 days with a subsequent change in therapy to rifaximin 400 mg twice daily for 14 days | |
| **Additional Recurrences** | |
| IVIG 400 mg/kg every 3 weeks for 3 doses, fecal transplantation therapy, rifaximin, nitazoxanide, probiotics, suppressive therapy with oral vancomycin for elderly patients and those with multiple comorbidities | |

IVIG = intravenous immunoglobulin
Data extracted from Kelly and LaMont[1]; Leffler and LaMont[2]; Jaber et al[16]; Gerding et al.[17]

for refractory disease.[1,2,16,17] In one oral vancomycin–tapering strategy, doses of 125 mg are given every 6 hours for 7 days, then 125 mg every 12 hours for 7 days, then 125 mg daily for 7 days, then 125 mg every other day for 8 days, and finally 125 mg every 3 days for 15 days. Another pulsed-dose regimen comprising oral vancomycin 125 mg every 6 hours for the initial 2 weeks followed by 125 mg 3 times a week for an additional 4 weeks has been successful in treating some cases of CDI recurrence.[2,11,17,20]

### Multiple Recurrences and Resistant Disease

For multiple recurrences of CDI, the disease process can be disabling and require alternative approaches to treatment. Probiotics have been used in the prevention of antibiotic-associated diarrhea; however, efficacy data for *Lactobacillus* and *Saccharomyces boulardii* for prevention of CDI are mixed. Used as monotherapy, none of the probiotics has been shown to be effective in treating CDI, but these agents may be considered as adjunctive therapy. A slight risk for bacteremia or fungemia exists with the use of probiotics in critically ill, immunocompromised patients. Rifaximin and nitazoxanide have also been considered for use in controlling recurrent CDI but are not FDA approved for this indication.[17] Fecal transplantation therapy using a blended fecal filtrate (usually, donated stool from a relative) with delivery via colonoscope or nasogastric tube has also been reported to be effective. In patients with severe CDI that is refractory to medical therapy, immunoglobulin therapy at a dose of 400 mg/kg IV every 3 weeks for three doses can be considered.[1]

## CONCLUSION

Nosocomial *C difficile* infections have become a major issue for patients in residential health care settings and hospitals; *C difficile* also affects patients who have been treated with antibiotics in the recent past. Although resistance to metronidazole and vancomycin is not common, novel epidemic strains of *C difficile* that are associated with greater morbidity and mortality are emerging. Consistent infection control measures are imperative to prevent spread of CDI. Recognition of fulminant disease early in the course of infection—along with resultant implementation of more aggressive supportive measures, use of oral vancomycin for severe disease, and early

surgical consultation for possible colectomy—improves survival rates for patients with severe CDI. For recurrent disease, retreatment with vancomycin or metronidazole is effective; however, additional recurrences of CDI may require novel approaches. □

*The views expressed in this article are those of the authors and do not necessarily reflect those of the US government or any of its agencies. Work completed on this article is independent of Dr. Morris' capacity as a federal employee.*

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