Current Strategies for Management of Initial Clostridium difficile Infection

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In the past decade, an epidemic strain of Clostridium difficile has led to increased incidence and severity of nosocomial C. difficile infections (CDI). Responsiveness to standard antimicrobial care for this strain is declining, and the morbidity and mortality of CDI and recurrent CDI are rising. Effective management requires a coordinated effort among all members of the healthcare team to facilitate early identification of patients at risk for CDI, early recognition of disease onset and confirmatory testing, prompt initiation of the most appropriate management approach, and ongoing monitoring throughout the continuum of care. Hospitalists, as coordinators of patient care, are in an ideal position to ensure that patients receive prompt and optimal treatment based on current clinical evidence and severity of the disease. Journal of Hospital Medicine 2012;7:S5–S10 © 2012 Society of Hospital Medicine

The incidence and severity of Clostridium difficile infections (CDI) have increased steadily over the past decade, paralleling the emergence of an epidemic strain of C. difficile in North America, the North American pulsed field type 1 (NAP1), restriction-endonuclease analysis type BI, polymerase-chain-reaction ribotype 027, commonly referred to as NAP1/B/027. The reduced responsiveness of CDI to standard antibiotic therapy, and increased death rate attributable to CDI, present a significant challenge to clinicians.1 This is a brief review of clinical strategies for effective management of initial CDI for hospital-based physicians.

Effective management of CDI requires a multidisciplinary effort that includes identification of patients at risk, rapid implementation of contact isolation for patients suspected of having CDI, and implementation of early and appropriate treatment based on current clinical evidence.2 Early recognition is, in large part, based on suspecting CDI anytime a patient develops antibiotic-associated diarrhea. An understanding of traditional and emerging risk factors for CDI can help clinicians identify this serious condition early.

CASE STUDY

A.L. is an 87-year-old woman in a rehabilitation facility who is recovering from left hip replacement surgery performed 3 weeks ago. Her past medical history is positive for heart failure, atrial fibrillation, type 2 diabetes mellitus, and chronic obstructive pulmonary disease. During her hospitalization, she was treated preoperatively with cephalexin for prophylaxis. She was recently started on ciprofloxacin for a urinary tract infection, and has been taking this for 6 days.

During morning rounds, her nurse reports that A.L. has had diarrhea for 2 days. She is currently afebrile, and her white blood cell (WBC) count is 11,400/μL. Ciprofloxacin was discontinued and a stool test for C. difficile toxin was ordered.

RISK FACTORS FOR CDI

The risk of developing CDI depends on 3 groups of factors: impairment of colonization resistance, risk of exposure to toxigenic C. difficile or its spores, and host health and immune status.

Impairment of Colonization Resistance

C. difficile is extremely common in the general environment. However, balanced intestinal microflora normally confer colonization resistance, a host factor that limits the proliferation of pathogenic microorganisms such as C. difficile.3 While colonization of C. difficile occurs in the community in only 1% to 4% of healthy adults, the rate of colonization in hospitalized adults is much higher, approximately 20% to 30%.4 Loss of normal resistance to C. difficile in adults is most commonly a consequence of antimicrobial therapy, which disrupts the intestinal microflora. The propensity of different antimicrobial agents to increase the risk for CDI varies due to differences in the complex relationship of their luminal concentrations, activity against C. difficile, and effects on the normal intestinal microflora.4 Almost every available antibiotic has been associated with CDI; however, broad-spectrum agents with antianaerobic activity appear to cause the greatest risk (Table 1).5 Second- and third-generation cephalosporins and fluoroquinolones are the most problematic because of their frequent use and high levels of resistance among strains of C. difficile to these agents.1,6–9 Regimens with multiple antibiotics and/or longer treatment courses are also associated with an increased risk.9

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Clinicians should be aware that while CDI usually presents during or shortly after initiation of the causative antimicrobial, onset may be delayed for 2 or 3 months. Healthcare professionals should consider CDI in patients who present with diarrhea and have a history of recent antimicrobial treatment in a hospital or as an outpatient. Other factors that may disrupt intestinal flora and lead to colonization by C. difficile include:

- Bowel preparation for colonoscopy or surgery.
- Cytotoxic chemotherapy.
- Colitis caused by inflammatory bowel disease.

**Risk of Exposure to Toxigenic C. difficile or Its Spores**

C. difficile spores, which are highly resistant to drying, temperature fluxes, and many common disinfectants, contaminate the patient care environment in hospitals and other healthcare facilities. They are viable for long periods and may be transmitted from the hands or fomites of healthcare personnel to patients. It is not surprising that this leads to a major infection control challenge.

**Host Health and Immune Status**

A healthy immune response to C. difficile and toxins A and B is associated with milder forms of the condition. Many patients colonized by pathogenic strains of C. difficile do not have symptoms; this “carrier state” is associated with high circulating titers of immunoglobulin G (IgG) antitoxin. Conversely, several important individual factors that increase the risk for CDI include advancing age, hospital admission, longer duration of hospital stay, severe underlying disease, impairment of immune function, suppression of gastric acid secretion (e.g., with proton pump inhibitors), enteral feedings (especially with use of a post-pyloric tube), and mechanical ventilation.

**RISK FACTORS FOR RECURRENT CDI**

The incidence of recurrent CDI within 60 to 90 days of initial CDI resolution following a course of treatment with metronidazole, vancomycin, or both is mostly 19% to 29%, but was 50% in 1 report. The risk for CDI recurrence increases with each recurrent episode: Patients with 1 prior episode of recurrent CDI have a >40% risk for an additional recurrence, and those with 2 or more episodes have a >60% risk. Two likely mechanisms that predispose patients to recurrent CDI are an inadequate immune response to C. difficile toxins and persistent disruption of the normal colonic flora due to therapy with metronidazole, vancomycin, or other concomitant antibiotics. Recurrent CDI is seldom due to resistance of vegetative cells of C. difficile to vancomycin or metronidazole. Two other important factors associated with recurrence are infection with a hypervirulent strain of C. difficile, and the fact that the current hospital population generally consists of older and sicker patients who have been treated with many broad-spectrum antibiotics.

Specific patient risk factors associated with recurrent CDI include:

- Previous history of recurrence.
- Increased age (>65).
- Severe underlying disease.
- Renal impairment.
- Conditions or treatments that lead to immunocompromise.
- Hospital admission (especially prolonged hospital stay).
- Use of additional antibiotics.

As noted above, ongoing treatment with antibiotics plays an important role in the risk for recurrence. Hu and colleagues found that concomitant antibiotic use after a diagnosis of CDI was associated with a 10-fold increased risk for recurrence (odds ratio [OR], 10.0; 95% confidence interval [CI], 1.5-68.3). Johnson and colleagues found that the rate of sustained response to CDI therapy, without subsequent recurrence, was higher in patients able to stop all other antibiotics and be treated with only fidaxomicin or vancomycin than it was in a group of patients treated with 1 of these agents plus an additional antibiotic (91.9% and 76.1%, respectively). In general, patients who require concomitant antibiotics have more comorbidities and are sicker, so the entire difference cannot be attributed to antibiotics. However, clinicians should carefully consider the ongoing need for antibiotics if CDI is suspected or confirmed.

Continued exposure to C. difficile in the hospital or home environment often leads to reinfection when vancomycin and metronidazole concentrations have decreased. Data show that at least half of clinical recurrences are reinfection with a different strain, and half are due to persisting intestinal infection with the original infecting strain. Therefore, patients with CDI should be educated about appropriate hygiene at home.

**TABLE 1. Propensity of Antimicrobials to Cause CDI**

<table>
<thead>
<tr>
<th>Very Commonly Related</th>
<th>Less Commonly Related</th>
<th>Uncommonly Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Other penicillins</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Sulfonamides</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Trimethoprim</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Ceftriaxone</td>
<td>Teicoplanin</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Moxifloxine</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloramphenicol</td>
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<tr>
<td></td>
<td></td>
<td>Tetracyclines</td>
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<tr>
<td></td>
<td></td>
<td>Carbapenems</td>
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<tr>
<td></td>
<td></td>
<td>Daptomycin</td>
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<td></td>
<td></td>
<td>Tigecycline</td>
</tr>
</tbody>
</table>

NOTE: See Bartlett, and Riddle and Dubberke. Abbreviation: CDI, Clostridium difficile.
CLINICAL MANIFESTATIONS OF CDI

CDI has a wide range of clinical manifestations, ranging from a mild and self-limited diarrheal illness to fulminant, life-threatening colitis. The onset of symptoms usually occurs within 3 to 7 days of antibiotic exposure, but may not arise for up to 10 weeks after stopping antibiotics. CDI is associated with watery diarrhea that is often accompanied by cramping abdominal pain and low-grade fever. Systemic symptoms generally increase with the degree of colitis. Patients with severe disease may also progress to having an ileus, or toxic megacolon or acute abdomen.

Up to 20% of critically ill patients have ileus or toxic megacolon, and therefore may not present with diarrhea; this, combined with a limited ability to communicate among some critically ill patients makes early diagnosis of CDI in this patient population extremely challenging. Therefore, physicians and other clinical staff must be vigilant about evaluating patients for the presence of CDI based on physical exam and laboratory findings. For example, fever, abdominal pain, and abdominal distention are likely to be present in patients with severe colitis. In addition, patients often have significant leukocytosis (often >20,000 cells/mm³) with bandemia. In advanced cases, an elevated serum lactate dehydrogenase may be seen—this is a nonspecific finding for gastrointestinal disease, but provides a clue to the presence of CDI. Because these findings often precede multiorgan dysfunction, the presence of CDI must be determined quickly and appropriate treatment initiated.

PRINCIPLES OF DIAGNOSIS

*C. difficile* infection should be suspected in patients with antimicrobial-associated diarrhea. Confirmatory testing should be performed, but only on watery or loose stools because the rate of symptomless colonization with *C. difficile* in hospitalized patients is high; a positive result on a normal stool sample proves only that the patient is colonized with *C. difficile*, but not necessarily infected. A notable exception is when CDI is suspected in a patient with ileus; as many laboratories will not accept solid stool for *C. difficile* testing, the clinician should notify the laboratory about the specific request and reasons for suspecting CDI.

Stool testing for eradication of *C. difficile* during or after therapy is not advised, as many successfully treated patients will continue to shed the organism and its spores. This symptomless carriage does not require additional treatment.

CASE STUDY CONTINUED...

A.L. was empirically started on oral metronidazole, 500 mg 3 times a day, pending results of the stool *C. difficile* test.

On rounds the following day, diarrhea was less frequent (decreased from 9 to 4 loose bowel movements in 24 hours). She reported mild abdominal discomfort and nausea, but was tolerating oral intake. Her temperature was 100.8°F.

Her lab results returned later in the afternoon were:

- WBC: 18,600 cells/µL.
- Potassium: 3.2 mEq/mL.
- Creatinine: 2.4 mg/dL (up from 1.1).
- Stool *C. difficile* test: negative.

There are a variety of tests for *C. difficile*, each with advantages and disadvantages (Table 2). Factors to consider when selecting a diagnostic test include turnaround time, sensitivity, specificity, cost, whether there is an ongoing outbreak, and the availability of particular tests. Recent guidelines for CDI management jointly developed by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) note that stool culture is the gold standard, but recognize the clinical limitations of its long turnaround time. Enzyme immunoassay (EIA) is noted to be “a suboptimal alternative approach for diagnosis” than the cell cytotoxin assay. Therefore, because EIA is most often used in clinical practice, it is important to be aware that a high clinical suspicion for CDI may warrant empiric therapy or repeat testing with a more sensitive test in a patient with an initial negative test result.

CURRENT STRATEGIES FOR CDI MANAGEMENT

While current guidelines recommend that treatment of CDI be based on disease severity, determination of...
severity is challenging, in part, because standard definitions are lacking and because the illness varies along a continuum of symptoms. In general, CDI can be categorized as: mild to moderate, severe, and severe disease with complications. Mild to moderate CDI is characterized by diarrhea and abdominal cramping, only without systemic symptoms. Severe CDI is distinguished by abundant diarrhea, severe abdominal pain/distension, leukocytosis, fever, or other systemic symptoms (Table 3). Patients with severe disease and other complications may present with a wide range of gastrointestinal symptoms accompanied by paralytic ileus, toxic megacolon, or other life-threatening conditions. CDI may progress in severity rapidly, even after initiation of treatment, so ongoing assessment of the patient’s condition and disease category is important.

In 2010, SHEA/IDSA published evidence-based guidelines for managing CDI based on severity of illness (summarized in Table 4). The first and most important step in the effective management of CDI in all patients, regardless of severity, is to discontinue the causative antibiotic(s). Data show that when all antibiotics are stopped, about 25% of patients with mild CDI who are otherwise healthy have resolution of diarrhea within 48 hours; most importantly, recurrent CDI is unlikely. Many hospitalized patients, especially in the intensive care setting, have serious concomitant infections, and therefore it may not be appropriate to discontinue the inciting antibiotic. In these patients, the regimen and available culture and sensitivity results should be thoughtfully reviewed, and change made when possible to a more narrow-spectrum regimen less likely to cause or exacerbate CDI (Table 1).

The next step, as discussed above, is to send a stool sample for *C. difficile* testing. Based on the patient’s clinical circumstances, the decision must be made whether or not to begin empiric therapy. In general, beginning treatment without testing for *C. difficile* is not recommended, because, at most, only about a third of hospitalized patients with diarrhea have CDI, even in an epidemic setting. If a patient is severely ill or has a rapidly deteriorating clinical course and is at high risk for CDI, empiric therapy may be appropriate while awaiting test results.

In patients with severe CDI and complications, reduced or absent bowel motility can reduce the amount of orally administered vancomycin that reaches the site of infection. Intracolonic administration of vancomycin may be indicated in these cases, or when oral therapy cannot be tolerated. Higher doses of oral vancomycin may also be used, with the goal of increasing fecal concentrations, however this strategy has not been studied. In all patients, antiperistaltic agents are usually avoided because of unproven concerns that they might mask symptoms and/or increase the risk for toxic megacolon.

Fidaxomicin, a new macrolide antibiotic in the macrolide group, has a narrow-spectrum and excellent activity against *C. difficile*. The US Food and Drug Administration approved fidaxomicin for treatment of adults for *C. difficile*–associated diarrhea (CDAD) in May 2011. Approval was based on 2 phase III trials involving 1105 patients with CDAD in which fidaxomicin was shown to have similar initial clinical efficacy and safety as vancomycin. In addition, more patients treated with fidaxomicin had a sustained response 25 days following discontinuation of treatment than patients treated with vancomycin. The recommended dosage of fidaxomicin is one 200-mg tablet orally twice daily for 10 days.

In a phase III trial (N = 596) of fidaxomicin (200 mg orally every 12 hours) versus vancomycin (125 mg orally every 6 hours) for 10 days, fidaxomicin was shown to be noninferior to vancomycin in achieving an initial clinical response and significantly better at preventing recurrent CDI. The rates of initial clinical response, the primary endpoint, and rates of recurrent CDI are shown in Table 5. The significant difference

### TABLE 3. Markers of Severe CDI

<table>
<thead>
<tr>
<th>Marker</th>
<th>Value</th>
<th>Reference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe diarrhea (&gt;10 bowel movements/day)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &gt;15,000 cells/µL</td>
<td>Associated with severe CDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &gt;25,000 cells/µL</td>
<td>Increased fatality</td>
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<tr>
<td>High or rising (50%) increase serum creatinine, or creatinine &gt;2 mg/dL</td>
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<td></td>
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<tr>
<td>Low serum albumin (&lt;2.5 mg/dL)</td>
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<td></td>
<td></td>
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<tr>
<td>Severe abdominal distension, pain</td>
<td></td>
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<tr>
<td>Ileus or toxic megacolon</td>
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<tr>
<td>Colonic thickening on CT scan</td>
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<td>Ascites on CT scan</td>
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<tr>
<td>Pseudomembranes on endoscopy</td>
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<tr>
<td>Hemodynamic instability</td>
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<tr>
<td>Organ failure</td>
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</tbody>
</table>

NOTE: See Johnson et al., McMaster-Baxter and Muhaier, Do et al., Kyne et al., Johnson et al., and Wilcox et al.

Abbreviations: CDI, *Clostridium difficile*; CT, computed tomography; WBC, white blood cells.

### TABLE 4. SHEA/IDSA Initial CDI Treatment Recommendations Based on Clinical Severity

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Supportive Laboratory Data</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>WBC &lt;15,000 cells/µL or serum creatinine &lt;1.5 times premorbid level</td>
<td>Metronidazole 500 mg orally 3 times per day for 10-14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC &gt;15,000 cells/µL or serum creatinine &gt;1.5 times premorbid level</td>
<td>Vancomycin 125 mg orally 4 times per day for 10-14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Hypotension or shock, ileus and/or megacolon; organ failure (eg, ARDS, coagulopathy)</td>
<td>Vancomycin 500 mg 4 times per day orally or by nasogastric tube plus metronidazole 500 mg IV every 8 hr</td>
</tr>
</tbody>
</table>

NOTE: See Cohen et al.

Abbreviations: ARDS, acute respiratory distress syndrome; CDI, *Clostridium difficile*; N, intravenous; SHEA/IDSA; Society for Healthcare Epidemiology of America; Infectious Disease Society of America; WBC, white blood cells.
in recurrence may be explained by the fact that metronidazole and vancomycin impact commensal microflora populations that normally mediate competitive exclusion of C. difficile. Compared with vancomycin, fidaxomicin has less effect on the composition of the fecal microbiota, in particular some clostridial clusters and Bifidobacterium. While acquisition costs for this new antibiotic are a consideration, they may be offset by a reduction in recurrent CDI, especially in high-risk patients.

**FOCUS ON FULMINANT/REFRACTORY CDI**

Management of CDI that is fulminant and/or refractory can be extremely challenging. In clinical practice, these conditions often overlap. Clinical characteristics that may help identify fulminant CDI include abdominal pain and tenderness, colonic distension, and signs of sepsis. Diarrhea may be absent or minimal due to ileus. Furthermore, a diagnosis of CDI is easy to miss, as these symptoms are also consistent with ischemic bowel or a perforated viscus. Gentle, flexible sigmoidoscopy or colonoscopy (without bowel preparation and with minimal air insufflation) may be extremely valuable to allow for immediate identification of pseudomembranous colitis, which speeds appropriate medical and surgical management.

First-line treatment for fulminant or refractory CDI is oral or intragastric vancomycin 500 mg every 6 hours. Intravenous (IV) metronidazole 500 mg every 6 hours should be added to the treatment regimen in those with ileus or megacolon. For patients with complete ileus, vancomycin can be administered rectally as 500 mg in 100 mL of normal saline every 6 hours. Normal pooled IV immunoglobulin has been used with mixed success, in patients with fulminant and/or refractory CDI, in an attempt to avert surgery or death by providing passive immunotherapy against C. difficile toxins A and B. In a study of monoclonal antibodies to toxins A and B that included 200 patients, recurrence rates among those with the epidemic NAP1/BI/027 strain were 8% for the antibody group and 32% for the placebo group (P = 0.06); in a subset with more than 1 previous episode of CDI, recurrence rates were 7% and 38%, respectively (P = 0.006).

Some patients with fulminant or refractory CDI are best managed with subtotal colectomy, which may be lifesaving. However, the optimal timing of surgery is difficult to establish, and the decision to proceed with this course can be difficult because patients with severe CDI are typically poor surgical candidates. Delaying surgery until the development of a systemic inflammatory response syndrome with concomitant severe disease, such as multisystem organ failure, immunocompromise, or hemodynamic instability, usually results in a poor outcome. The best approach is to get a surgical consult early, when the course of CDI starts to deteriorate, so that management decisions can be based on input from a multidisciplinary team of clinicians.

**CASE STUDY CONTINUED...**

A.L. was subsequently transferred to an acute care facility. Her therapy for C. difficile was switched to oral vancomycin, 125 mg 4 times daily. On arrival in the emergency department, the following findings were noted:

- No further diarrhea, but abdominal distention noted.
- Temperature: 101.4°F.
- Fall in blood pressure (BP) to 90/48 mmHg during transfer, which responded to a fluid bolus, and increased to 108/74.
- WBC: 27,000/μL.
- Abdominal computed tomography (CT) showed thickening of descending and sigmoid colon, and the rectum.
- Proctoscopy confirmed pseudomembranous colitis.

Oral vancomycin was increased to 500 mg 4 times daily, and IV metronidazole 500 mg every 8 hours was added. C. difficile infection responded to this...
regimen and she was subsequently discharged to home care.

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