**Clostridium difficile—Associated Diarrhea**

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**STATE-OF-THE-ART CLINICAL ARTICLE**

_Clostridium difficile_ is well recognized as the major, if not the only, important cause of infectious diarrhea that develops in patients after hospitalization in the United States, and likely, in developed countries around the world [1]. The temporal relation between the onset of _C. difficile_-associated diarrhea (CDAD) and prior or concurrent antimicrobial therapy has caused confusion regarding the pathogenesis of this disease and has led to consideration of this infection as distinct from other enteric diarrhea syndromes such as salmonellosis or shigellosis. Specifically, the understanding of some clinicians and infection control practitioners is that _C. difficile_, which in small numbers is part of the normal intestinal flora, subsequently proliferates or overgrows because of suppression of the other indigenous bowel flora by antimicrobials. Our current understanding of the pathogenesis of CDAD is that _C. difficile_, like virtually all other enteric pathogens, is acquired exogenously and that a variety of clinical outcomes ensue following infection, ranging from asymptomatic colonization to diarrhea to more-severe disease syndromes. The unique aspects of this enteric pathogen are its important reservoirs of infection (e.g., hospitals and chronic care facilities) and its nearly complete dependence on prior disruption of the “infection resistance” provided by the indigenous microflora of the intestine, which occurs when antimicrobial therapy is administered.

**Epidemiology of CDAD**

In the setting of endemic or epidemic CDAD, surveillance cultures performed for all patients on the affected hospital ward(s) will identify asymptomatic _C. difficile_ fecal excretors or carriers [2, 3]. In fact, asymptomatic carriers usually outnumber symptomatic patients by several fold, as is the case with other enteric diseases such as cholera. While colonization of healthy, nonhospitalized adults by _C. difficile_ is uncommon, the rate of colonization among hospitalized adults is often >20% for those hospitalized >1 week. Some of these patients are colonized on admission, but for patients whose cultures are initially negative for _C. difficile_, the risk of acquiring the organism increases in direct proportion to length of hospital stay. In one study, the rate of acquisition was 13% for patients hospitalized 1–2 weeks, and it increased to 50% for those hospitalized >4 weeks (figure 1) [4]. In addition, asymptomatic carriage of _C. difficile_ in healthy neonates is very common, although rates of carriage decrease markedly during the first year of life. Carriage rates for neonates vary significantly among different nurseries, and the data suggest that _C. difficile_ is acquired nosocomially in this setting rather than via the intestinal flora of the mother.

Although other reservoirs of _C. difficile_ (including numerous animal species) likely exist outside hospitals, the incidence of community-acquired CDAD (7.7 cases per 100,000 person-years of observation) is low [5]. Risk per antibiotic exposure period (defined as 42 days) is also low (6.7 cases per 100,000 risk exposures) [5]. Although CDAD is rarely diagnosed in the outpatient setting, there is concern that diagnostic testing may not be performed sufficiently in this setting to detect CDAD and that diagnostic efforts may not be focused on the proper patients—i.e., those receiving antimicrobials. In Australia, Riley and colleagues [6] found that the rate of detection of _C. difficile_ in submitted specimens increased from 2.6% to 10.7% after an educational program was instituted to encourage general practitioners to include testing for _C. difficile_ when outpatients presented with diarrhea. Similar data for the outpatient setting in the United States are lacking at a time when the use of antimicrobials in this setting is increasing.

Antimicrobial therapy was associated with the development of pseudomembranous colitis even before _C. difficile_ was recognized as the etiologic agent, and this association between antimicrobial agents and _C. difficile_ disease remains nearly universal. Although the disease is a toxin-mediated bacterial infection, almost all affected patients have recently been treated with antimicrobials or, occasionally, chemotherapeutic agents for cancer. Clindamycin, ampicillin, and cephalosporins have been most frequently associated with the development of pseudomembranous colitis, whereas parenteral aminoglycosides, vancomycin, and metronidazole have been infrequently implicated. In a large outbreak in the United Kingdom, 76.3% of 169 patients with _C. difficile_ infection had received cephalosporins [7]. Presently, third-generation cephalosporins such as ceftriaxone, cefotaxime, and ceftazadime have been implicated.
The outcome after treatment of asymptomatic carriers susceptibility or immunity, to the virulence of the particular Clostridium difficile. Eradication of this hypothesis is true, such asymptomatic carriers would be Prospective observations suggest that the majority of patients when they are exposed to antimicrobial therapy (figure 2A). If colonized patients are at increased risk for CDAD, particularly those given placebo despite the fact that fecal drug concentrations of ≥1,000 μg/g of stool were achieved during treatment. We interpret this to be a result of ongoing exposure to C. difficile and of increased susceptibility to C. difficile infection because of bowel flora disruption following vancomycin treatment.

Contrary to the hypothesis that colonized patients are at increased risk for developing CDAD, our initial prospective study of C. difficile acquisition and disease did not indicate that asymptomatic carriers were at increased risk [2]. Data from four similar longitudinal studies that included 618 noncolonized patients who were followed up for 1,066 weeks and 192 colonized patients who were followed up for 282 weeks showed that colonized patients were actually at decreased risk of subsequent CDAD [10]. In that analysis colonization was defined as primary asymptomatic colonization to differentiate patients with this condition from those who may have been culture positive after resolution of CDAD—a group in which the recurrence of diarrhea is common. Many of the patients with primary asymptomatic colonization were colonized with non-toxigenic strains, but 56% were colonized with virulent, toxigenic strains, and nine of the 12 specific types of C. difficile responsible for CDAD in other patients were found in the asymptotically colonized group.

As a result, we have derived an alternative model of pathogenesis for infection with C. difficile (figure 2B). We hypothesize that a patient is admitted to a hospital and is at negligible risk for CDAD until an antimicrobial agent is administered. If during or after treatment such a patient is subsequently exposed to C. difficile, the patient either develops CDAD after a short incubation period of a few days or becomes colonized without diarrhea, or, potentially, does not become infected at all. Our data from the four longitudinal studies indicate that once established as an asymptomatic carrier, a patient is at decreased risk for CDAD. Patients appear to be continually at risk of exposure to C. difficile throughout hospitalization (figure 1) and become vulnerable to infection only after they have been exposed to antimicrobials.

Thus, CDAD can be viewed as at least a “three-hit” disease [12]. Two components appear to be essential: first, exposure to antimicrobials, and second, exposure to toxigenic C. difficile. Prospective observations suggest that the majority of patients do not become ill following the first two “hits.” The presence of at least one additional factor appears to be necessary for CDAD to occur. The additional factor may be related to host susceptibility or immunity, to the virulence of the particular...
The rapidity with which vancomycin-resistant enterococci (VRE) have spread in health care facilities is indicative of the difficulty in preventing and controlling the spread of *C. difficile* in these same institutions. Both of these nosocomial problems are characterized by similar epidemiological characteristics, including asymptomatic gastrointestinal carriage, contamination of the environment, and contamination of the hands of personnel. Similarly, the risks of infection with either organism are increased in association with increased length of hospitalization; advanced age; severity of underlying illness; prior use of antimicrobials, including third-generation cephalosporins; use of electronic rectal thermometers; and use of enteral feedings [18]. Similar control and prevention strategies have been
used for infections caused by both VRE and *Clostridium difficile*; these strategies include barrier-isolation precautions of various types to prevent horizontal transmission of the organism and controls on the use of certain antimicrobials to reduce the risk of colonization and infection. Unfortunately, it is difficult to ensure compliance with these types of recommendations, a factor that may explain the limited success of control and prevention measures to date.

Two sets of guidelines for the prevention and control of *Clostridium difficile* infection have been published [19, 20]. The guidelines from the American College of Gastroenterology (ACG) and the Society for Healthcare Epidemiology of American (SHEA) are summarized and compared in table 1. These guidelines differ substantively only in the inclusion of a disinfection product recommendation and education recommendation from the ACG and a recommendation regarding replacement of electronic thermometers from SHEA. Justification for and strength of the recommendations is provided in the SHEA document, and the ACG guidelines provide a detailed discussion of infection control issues. Other preventive strategies are under evaluation, including induction of passive immunity by oral administration of *Clostridium difficile* antibodies, use of vaccines against *Clostridium difficile* or its toxins, and development of biological interference methods of various types.

### Diagnosis and Treatment

An optimal laboratory test for CDAD remains to be developed, although progress has been made on the question of clinical selection of patients to be tested for CDAD. A rule for laboratory testing of hospitalized patients for CDAD (defined in the laboratory as a positive cell cytotoxin assay) has been derived and validated in the clinical setting. This rule is that testing of stool for *Clostridium difficile* cytotoxin should be done only for hospitalized adults with both prior antimicrobial use (within 30 days) and one or both of the following symptoms: significant diarrhea (at least three watery or unformed stools in 24 hours) or abdominal pain [21, 22]. The major benefit of this rule is that it has a very high negative predictive value (94%–97%) for patients who do not meet the criteria for testing, which would negate or defer the need for 29%–39% of the cytotoxin tests ordered. Testing can still be performed later for the few patients whose CDAD is not diagnosed by using this strategy if their symptoms persist or worsen.

The fundamental issue of the lack of a single laboratory test that is both sensitive and specific for diagnosing CDAD remains unresolved and has been summarized in prior reviews [19, 20, 23]. The most specific test, the cell cytotoxin assay, and the most sensitive test, stool culture for *Clostridium difficile*, are both associated with relatively slow turnaround times; both require a minimum of 2 days to yield results. Even in laboratories where both of these tests are performed to obtain maximal sensitivity and specificity, results cannot be obtained rapidly. More rapid tests (those requiring 2–4 hours to perform), such as the EIA for detecting toxin A or toxins A and B, are very specific but somewhat less sensitive than the cell cytotoxin assay, and if these tests are batched and not run daily in the laboratory, the results may not be reported faster. Tests that detect only toxin A may miss a small but increasingly reported number of *Clostridium difficile* isolates that produce toxin B but not toxin A [24]. The most rapid test, latex agglutination, which tests for the presence of glutamate dehydrogenase (not toxin), is neither sensitive nor specific, and like culture, does not distinguish toxigenic from nontoxigenic *Clostridium difficile* [25].

Practice recommendations regarding the diagnosis of CDAD from the two published sets of guidelines emphasize different
The diagnosis of *Clostridium difficile*–associated diarrhea (CDAD) should be suspected in any patient with diarrhea who has received antibiotics within the previous 2 months and/or whose diarrhea began >72 hours after hospitalization.

When the diagnosis of CDAD is suspected, a single stool specimen should be sent to the laboratory for testing for the presence of *C. difficile* and/or its toxins.

If the results of those tests are negative but diarrhea persists, one or two additional stool samples can be sent for testing with the same or different tests.

Endoscopy is reserved for special situations, such as when a rapid diagnosis is needed and test results are delayed or the test is not highly sensitive, or the patient has ileus and a stool sample is not available, or when other colonic diseases are included in the differential diagnosis.

### Table 2. Practice guidelines for the diagnosis of *Clostridium difficile*–associated diarrhea.

<table>
<thead>
<tr>
<th>American College of Gastroenterology recommendations*</th>
<th>Society for Healthcare Epidemiology of America recommendations²</th>
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<tr>
<td>1. The diagnosis of <em>C. difficile</em>–associated diarrhea (CDAD) should be suspected in any patient with diarrhea who has received antibiotics within the previous 2 months and/or whose diarrhea began &gt;72 hours after hospitalization.</td>
<td>1. It is recommended that tests for <em>C. difficile</em> or its toxins be performed only on diarrheal (unformed) stool specimens unless ileus due to <em>C. difficile</em> is suspected.</td>
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<tr>
<td>2. When the diagnosis of CDAD is suspected, a single stool specimen should be sent to the laboratory for testing for the presence of <em>C. difficile</em> and/or its toxins.</td>
<td>2. Testing of stools of asymptomatic patients for <em>C. difficile</em> or its toxins is not clinically useful (including ‘‘tests of cure’’) and is not recommended except for epidemiological investigation purposes.</td>
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<tr>
<td>3. If the results of those tests are negative but diarrhea persists, one or two additional stool samples can be sent for testing with the same or different tests.</td>
<td>3. Clinical illness usually does not correlate with the presence of <em>C. difficile</em> or its toxins in the stools of infants &lt;1 year old; testing of these patients is discouraged.</td>
</tr>
<tr>
<td>4. Endoscopy is reserved for special situations, such as when a rapid diagnosis is needed and test results are delayed or the test is not highly sensitive, or the patient has ileus and a stool sample is not available, or when other colonic diseases are included in the differential diagnosis.</td>
<td>4. Stool culture is the most sensitive test for CDAD, whereas the stool cell cytotoxicity assay (toxin B) is the most specific; for maximal diagnostic sensitivity and specificity, performance of both tests is recommended.</td>
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<td>* Data are from [20].</td>
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Aspects of diagnosis (table 2). As the basis for suspecting a diagnosis of CDAD, the ACG recommendations emphasize a history of antibiotic use within 2 months before the onset of diarrhea and the onset of diarrhea >72 hours after hospitalization. The SHEA recommendations emphasize testing only diarrheal stools and advise against testing asymptomatic patients and young children. The latter recommendation against testing children with diarrhea for the presence of *C. difficile* toxin is supported by the results of a clinical trial of the efficacy of toxin B detection for 618 children (median age, 21 months) with diarrhea and 135 controls (median age, 18 months) [26]. Toxin was found in 4.2% of specimens, but its presence did not correlate with the diarrheal symptoms in either inpatients or outpatients.

The remainder of the SHEA and ACG recommendations focus on the relative merits of the types of tests available and strategies for testing, including submission of multiple stool specimens; this latter strategy partially overcomes the lack of sensitivity of the cell cytotoxin assay but adds further delay in making a diagnosis [27]. These latter recommendations result from the current lack of a single rapid, sensitive, and specific test and are likely to change when such a test becomes available.

The question of the utility of the test for fecal leukocytes or the stool lactoferrin test in screening for CDAD has been raised. The sensitivity (60%–75%) of these tests in studies that have demonstrated the highest percentage of positive tests in cytotoxin-positive specimens is also accompanied by a high rate of positivity in cytotoxin-negative stools (30%–39%) [27–29]; thus, in our opinion, these tests are not sufficiently sensitive or discriminatory to serve as good screening tools for CDAD. Since neither a positive nor negative result of the fecal leukocyte test will obviate the need to do specific testing for *C. difficile* or *C. difficile* toxin, it seems more efficient to simply bypass the fecal leukocyte test and order a more specific *C. difficile* toxin assay for patients who have received antibiotics and develop diarrhea in the hospital.

Although most patients will require specific therapy, it should be remembered that CDAD is a complication of antimicrobial therapy and that discontinuation of the offending agent may be the only intervention necessary. Diarrhea will resolve without specific antimicrobial therapy in 15%–23% of patients with CDAD [30, 31]. Metronidazole, vancomycin, teicoplanin, and fusidic acid are all effective therapeutic agents for CDAD, but most clinical experience has been with metronidazole and vancomycin. Metronidazole is presently considered the initial drug of choice (despite the fact that the U.S. Food and Drug Administration has not approved it for this indication) because of clinical efficacy that is comparable to that of vancomycin [31, 32], because of lower cost, and because of concern over spread of glycopeptide resistance to other pathogens such as enterococci. However, the high degree of intestinal absorption of metronidazole and the inability to detect it in the stools of treated, asymptomatic patients has caused concern about its use. Bactericidal fecal concentrations of the drug are present in patients with CDAD, but these concentrations decline as the...
diarrhea decreases. Possible explanations for this observation include the secretion of metronidazole directly through inflamed mucosa during episodes of diarrhea or incomplete absorption of the drug during episodes of diarrhea because of rapid intestinal transit time.

In addition to two randomized, controlled studies, there has been a study of >600 patients at one institution who were treated for CDAD with metronidazole; the drug intolerance rate, treatment failure rate, and relapse rate were 1%, 2%, and 6%, respectively [30]. Oral therapy with either metronidazole or vancomycin for 10 days is effective in >95% of patients [19]. Therefore, we recommend the following therapeutic regimens, given orally for 10 days: first choice, metronidazole, 250 mg four times daily or 500 mg three times daily; alternative choice, vancomycin, 125 mg four times daily [19, 20, 32]. No diagnostic testing at the end of treatment or as follow-up is recommended unless symptoms (almost always diarrhea) recur.

Although most patients respond to specific therapy, 5%–30% of patients will develop recurrent CDAD, usually within 1 or 2 weeks after treatment for the original episode has been discontinued [19]. Recurrence of diarrhea may be caused by a relapse due to the original organism or reinfection by a new *C. difficile* organism. Stool testing for CDAD should be performed to document recurrence before retreatment is instituted. Diarrheal recurrences are not due to the development of antimicrobial resistance, and patients typically respond again to the agent used to treat the original episode [30]. A small number of patients develop multiple recurrences; they respond to specific therapy each time but develop recurrent symptoms and have positive stool cytotoxin assays after completion of a course of treatment with metronidazole or vancomycin.

A variety of empirical approaches have been used to treat patients with CDAD, including biotherapeutic measures; the rationale of such measures is to avoid further antibiotic therapy and allow the normal colonic flora to reestablish itself. They include administration of *Saccharomyces boulardii* or *Lactobacillus* species, rectal infusion of feces or a synthetic fecal bacterial flora, and the administration of a nontoxigenic *C. difficile* strain. Additional strategies have involved administration of vancomycin and rifampin in combination, vancomycin in tapering doses, cholestyramine, and intravenous gamma globulin; whole-bowel irrigation; and withholding of all treatment with careful observation [19]. Our personal preference for the treatment of multiple relapses is the combination of vancomycin plus rifampin for 10 days, as originally described by Buggy et al. [33], but no critical comparative data, other than those for the use of *S. boulardii* (which is not approved for use in the United States) on the efficacy of treatment of CDAD recurrences are available [34].

Toxic megacolon is the most serious manifestation of *C. difficile* infection and, paradoxically, may present in the absence of diarrhea. In addition, some cases may be precipitated by the use of antimotility agents such as diphenoxylate and loperamide. These agents are contraindicated for the treatment of *C. difficile* colitis as well as other inflammatory or invasive diarrheal syndromes. As is the case with treatment of multiple recurrences, treatment is empirical when the oral route is not reliable. Attempts to achieve effective antimicrobial concentrations at the site of infection have included administration of intravenous metronidazole, administration of vancomycin by either rectal enema or placement of a long catheter in the small intestine, or combinations of these regimens [30]. Finally, surgical intervention is indicated for patients with toxic megacolon who do not respond to medical treatment or for those with suspected colonic perforation. A variety of procedures have been performed, but subtotal colectomy with sparing of the distal rectum may be the preferred surgical option [35].

### Summary and Unresolved Problems

Declining hospital admission rates and shorter hospital stays have resulted in a reduction in the likelihood that patients will acquire CDAD, but the increased severity of illness of patients in hospitals and the higher rate of immunosuppression among these patients has resulted in an increased proportion who are receiving antimicrobials and are thus at increased risk of CDAD. Although a circumstance not well studied in the United States, patients in the community may also be at increasing risk of developing CDAD when they are treated with antimicrobials at home; this is an observation that has been made for Australian patients but has not been duplicated in other patient populations [6].

It seems clear that three major issues continue to plague physicians and infection control practitioners with respect to the management of CDAD. The first issue is the lack of a rapid, sensitive, and specific test for CDAD; the second is the relative inability to control and prevent CDAD in hospitals and institutions; and the third is the inability to treat patients effectively because of the problem of disease recurrence. The availability of more-rapid and more-sensitive diagnostic tests will enable clinicians to diagnose CDAD more accurately and in a timely fashion. Breakthroughs in this area are likely to come through the use of more-sensitive monoclonal antibody test systems that detect both toxin A and toxin B or through the use of PCR with primers from the toxin A and toxin B sequences of *C. difficile*.

The second issue, CDAD prevention and control, requires new and innovative approaches beyond that of traditional infection control-barrier methods. It may be possible to exert much more influence on the rates of CDAD by focusing on antimicrobial use patterns in hospitals. It has certainly been shown with clindamycin that control of the use of this agent can rapidly eliminate a CDAD outbreak [9]. It is likely that other antimicrobial agents or groups of agents are similarly closely linked to CDAD rates and that by use of risk analysis, the role of other antimicrobials such as extended-spectrum cephalosporins may be more frequently identified and the use of these agents controlled to successfully lower CDAD rates [36]. Indeed, it be-
hooves all prescribers of antimicrobials to be certain of the necessity to treat with an antimicrobial and to practice good antimicrobial stewardship by minimizing the duration of therapy and the number of antimicrobials prescribed. Other preventive strategies also are in need of exploration, including development of a vaccine that can be effectively and quickly administered in the hospital setting or development of various means of biological interference that can quickly restore natural resistance to \textit{C. difficile} in patients who receive antimicrobials.

The third problem, recurrence of disease, appears to be largely a result of the method used to treat CDAD. The treatment of CDAD—a disease that is acquired only after receipt of an antimicrobial—with yet another antimicrobial (vancomycin or metronidazole), which is highly effective at relieving symptoms, renders a patient susceptible to another bout of CDAD for an unknown period after treatment. This susceptibility is presumably mediated by the effect of antimicrobial agents on the bowel flora, and recurrence may be due either to the original strain of \textit{C. difficile} or a new strain, especially if a patient remains in the same high-risk hospital environment. Treatment methods that substitute for or supplement the use of an antimicrobial to treat CDAD are needed if we are to decrease recurrence rates. Use of \textit{S. boulardii} as a supplement has been highly successful in reducing recurrences [34], but the treatment is lengthy and not yet available in the United States. Other immunologic or biological methods, including use of passive antibodies and nontoxicogenic \textit{C. difficile}, need to be explored as means of preventing recurrences [37].

Finally, we believe it is appropriate to view CDAD as yet another antimicrobial use-resistance problem, not unlike infection due to VRE or methicillin-resistant \textit{Staphylococcus aureus}. The epidemiology and risk factors for infection due to VRE appear to be similar to those for CDAD [18]. The costs associated with CDAD have been reviewed for a group of Australian patients; these patients had hospital stays that were 18 days longer than those for matched controls [38]. Certainly, if the added length of stay is attributable to CDAD, then there is enormous monetary benefit to hospitals to work to reduce their CDAD rates, not to mention the benefit to patients in terms of the reduction of the pain, suffering, and mortality that result from this infection as well as other nosocomial infections.

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References


Additional Suggested Reading

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