A formerly infrequently isolated strain of *Clostridium difficile* known as BI/NAP1 has resulted in geographically diverse outbreaks of *C. difficile*–associated disease. Such rapid dissemination and distribution of an outbreak strain of *C. difficile* are unprecedented, with many regions across North America, as well as several countries in Europe, being affected, all in such a short period of time. Also of note is that nontraditional hosts (e.g., otherwise healthy, noninstitutionalized persons residing in the community, some without antimicrobial exposure) have been reported to have severe disease. Data suggest that certain virulence characteristics may be responsible for more severe clinical presentations and poor outcomes. These factors (e.g., hypertoxin production, hypersporulation, antimicrobial resistance) possessed by a previously uncommon strain of *C. difficile*, in conjunction with particular host and environmental factors, may have precipitated the now widespread establishment of this pathogen. Antimicrobial intervention has traditionally been a mainstay of combating *C. difficile*–associated disease. Efforts to combat BI/NAP1 should include good antimicrobial stewardship in addition to effective infection control and environmental intervention.

**Key Words:** *Clostridium difficile*, BI/NAP1, antimicrobial stewardship, adverse events.

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The organism first termed *Bacillus difficilis* in the mid-1930s, and now known as *Clostridium difficile*, continues to evolve into a formidable pathogen. *Clostridium difficile*–associated disease (CDAD) has traditionally ranged in presentation from self-limiting diarrhea to a fulminant, life-threatening disease. Of considerable interest is the observation that CDAD appears to be increasing worldwide in both incidence and severity of disease. Reasons for this are not entirely clear, are most likely very complex and interwoven, and may be due in part to the emergence of a previously uncommon strain of *C. difficile*. To better understand the implications of recent findings, it is fundamental to appreciate the fact that the risks for CDAD are complex and consist of exposure to toxigenic strains of the organism, previous use of any antimicrobial agent perhaps compounded by the previous use of antimicrobials that are specifically inactive or have borderline activity against *C. difficile*, exposure to gastric acid suppressants, poor host serum immunoglobulin levels, advanced age, and severity of underlying illness of the host. The sequence of these events is important for acquiring CDAD: first is exposure to antimicrobials, second is exposure to toxigenic strains of *C. difficile*, and third is the presence of additional factors just mentioned.
The organism responsible for the recently reported outbreaks in North America and Europe has been labeled BI/NAP1 and is distinguishable from previously identified outbreak (J-type) strains from the late 1980s and early 1990s. The BI/NAP1 strains of *C. difficile* produce greater amounts of toxins A (TcdA) and B (TcdB) carry an additional clostridial toxin termed a binary toxin, belong to toxinotype III, have an increased sporulation capacity, and are fluoroquinolone resistant. These characteristics differentiate BI/NAP1 from traditional *C. difficile* strains. It should be noted that whereas the predominant outbreak strain is BI/NAP1, additional non-BI/NAP1 strains have been identified in outbreak areas, to a lesser degree, and contain similar virulence characteristics as the current outbreak strains.

In addition to identified changes in the pathogen, certain augmenting host and environmental factors may be to blame. These include the fact that traditional hand washing with soap and water in hospitals has shifted to the preferential use of alcohol-based hand hygiene products in many institutional settings over the last 5–10 years (alcohol is ineffective against *C. difficile* spores). In addition, traditional hospital cleaning agents (quaternary ammonium–based products) do not kill *C. difficile* spores. In fact, quaternary ammonium–based cleaning agents have been shown to substantially increase the sporulation capacity of *C. difficile*. The greater severity of disease attributable to BI/NAP1 in combination with these environmental risk factors may be contributing to a cycle that has led to *C. difficile* outbreaks on at least two continents.

Both clinicians and health care administrators alike are concerned with the changes in the *C. difficile* landscape. In addition to the notable consequences of CDAD, this disease is burdening already taxed health care resources. For example, patients with CDAD have been shown to incur 54% greater costs and remain hospitalized for an average of 3.6 days longer than patients who do not develop CDAD during hospitalization. Furthermore, because of changes in environmental cleaning policies required during outbreak scenarios, additional expenditures are required to equip environmental services departments to prepare and handle 10% sodium hypochlorite (bleach) solutions or to purchase expensive commercially premixed hypochlorite-based products. Moreover, patients with CDAD in acute care facilities need to be isolated or cohorted, which may cause significant financial challenges related to bed management. This was exemplified best by ministry officials in Quebec who directed $20 million into hospital infection control resources and infrastructure changes to contain CDAD after more than 100 people died over a short period of time. This review provides an update regarding what has been learned about the emerging epidemic strain of *C. difficile*, followed by a practical review of one institution's challenges related to its presence.

The Changing Epidemiology of *Clostridium difficile*–Associated Disease

Incidence

The National Nosocomial Infections Surveillance (NNIS) system has reported an increasing trend in CDAD rates over the last 2 decades. In addition, one group of authors reported a 26% relative increase in 2001 over 1998–2000 in the annual proportion of discharges from nonfederal hospitals in the United States, with CDAD listed as any discharge diagnosis. Although a recent study performed at Prevention Epicenter Hospitals suggested no increase in CDAD rates between 2000 and 2003, their mean hospitalwide rates of 12.1 cases/10,000 patient-days or 7.4/1000 hospital admissions was 2–6 times greater than that reported from the NNIS system hospitals from 1987–2001 and teaching hospitals during the same period. Regardless of national rates that appear to be increasing, monitoring rates locally is of utmost importance.

Severity

In 2000, reports from the University of Pittsburgh noted increased CDAD incidence and severity as indicated by a doubling of disease rates along with an increased number of colectomies and deaths. In Canada, most notably the Sherbrooke region in Quebec, a CDAD outbreak attributable to BI/NAP1 resulted in excess mortality. The authors of a matched case-control study reported that 30-day mortality rates were 3-fold higher if CDAD complicated a patient's admission. In addition, prolonged hospitalizations, relapses, and readmissions characterized infection with *C. difficile* during this outbreak. Recently, reports of severe CDAD have surfaced in previously low-risk populations (otherwise healthy persons living in the community, some without a history of antibiotic exposure) in a four-state region.
The Pathogen: BI/NAP1

The strain BI/NAP1 has contributed to outbreaks in several regions of North America, the United Kingdom, and the Netherlands. It was identified and referred to by polymerase chain reaction as ribotype 27 (CD027), by pulsed-field gel electrophoresis as North American pulse-field type 1 (NAP1), by restriction-endonuclease analysis (REA) as group BI, and by toxinotyping as toxinotype III. Various publications may refer to the strain by different terms—BI/NAP1 or NAP1/027—but they are referring to the same strain. This current outbreak strain is distinct from that causing previous outbreaks during the late 1980s and early 1990s, known as the J strain (REA type J7/9). As previously mentioned, notable virulence characteristics associated with the BI/NAP1 strain include increased toxin production (TcdA and TcdB), the presence of a binary toxin, altered antimicrobial resistance patterns (fluoroquinolone resistance), and increased sporulation capacity.

Increased Toxin Production

The TcdA toxin has been termed “the enterotoxin,” as it is responsible for the expression of diarrhea and colonic inflammation, and TcdB “the cytotoxin,” which is responsible for actinomorphic changes in tissue culture cells. In all but rare cases, both toxins are expressed in patients with clinical disease; however, strains that are TcdA negative but TcdB positive have been identified. The toxins TcdA (308 kD) and TcdB (270 kD) are among the largest toxins to be harbored by bacteria and are encoded on a chromosome within the pathogenicity locus (PaLoc) of the organism. Also located within the PaLoc are regulatory genes such as tcdC, which is a downstream negative regulatory gene that controls the expression of TcdA and TcdB. All identified BI/NAP1 strains contain an 18-base pair tcdC gene deletion that is thought to be responsible for the accelerated kinetics of toxin production. Traditionally, TcdA and TcdB are produced most efficiently when the organism is in the stationary growth phase. In contrast, BI/NAP1 strains produce 16 times more TcdA and 23 times more TcdB, and studies indicate that most of this production occurs in the logarithmic growth phase (Figure 1).

Binary Toxin

In addition to the well-characterized TcdA and TcdB toxins, a formerly uncommon binary toxin has been identified in all of the BI/NAP1 isolates (previously found in approximately 6% of clinical isolates). The structure and function of this toxin are similar to those of other binary toxins, such as iota toxin found in Clostridium perfringens. Although patients infected with binary toxin–positive strains of C. difficile trended toward having greater disease severity, TcdA- and TcdB-negative but binary toxin–positive strains of C. difficile have been shown to be nonpathogenic in classic nonclinical models of infection. Thus, the pathogenic role of binary toxin in BI/NAP1 is unknown.

Toxinotyping

Clostridium difficile strains can also be classified by toxinotyping studies. Subtle sequence variations within the PaLoc account for the various toxinotypes of C. difficile, of
which there have been reported to be at least 22 different types. Toxinotype III, to which BI/NAP1 belongs, was previously rare, accounting for only 2–3% of clinical isolates. Whether toxinotyping can be used to distinguish virulence potential among strains has yet to be demonstrated.

Sporulation Capacity

Genotypically distinct strains of *C. difficile* have been shown to demonstrate a propensity to hypersporulate and have been reported to be responsible for previous outbreaks. The BI/NAP1 strain, like other outbreak strains, has demonstrated the capacity to hypersporulate compared with other nonoutbreak strains (Figure 2). This putative virulence characteristic may be, at least in part, responsible for its rapid establishment in many institutions where outbreaks have been reported. As with the other recently identified characteristics of this organism, future studies are required to elucidate the exact role of hypersporulation in the transmission or pathology of *C. difficile*.

The Environment

Experts have pointed out that blaming antimicrobial agents alone is too simplistic and that people often forget about the source of the bacterium. Both symptomatic and asymptomatic patients with *C. difficile* shed vegetative forms of the organism and spores into the environment. *Clostridium difficile* spores may persist on surfaces for years and remain a problematic source of environmental contamination and infection. Although intuitive, as levels of environmental contamination increase, so does the prevalence of *C. difficile* found on the hands of health care workers. Thus, susceptible patients may acquire the organism either directly from the hands of health care workers or circuitously from the environment.

Disease Severity

Among the factors that may be contributing to outbreaks of CDAD is the increased severity of disease associated with the BI/NAP1 strain. Greater frequency of diarrhea, surgery requirements, and recurrences would at least theoretically lead to an advantageous scenario for the establishment of the organism into the environment. In concert with hypersporulation characteristics, BI/NAP1 appears to be ideally suited for widespread dissemination and survival.

Alcohol-Based Hand Hygiene Products

The use of alcohol-based hand hygiene products in place of hand washing with soap and water in health care settings has become common and may be playing a role in the transmission of *C. difficile*. Alcohol is not sporicidal and is not efficient in removing *C. difficile* from the hands. In fact, an average 36% (range 18–60%) of the initial inoculation of *C. difficile* spores on a contaminated hand could be transferred by handshake after using commercially available alcohol gels. In contrast, the mechanical action of hand washing in a sink with soap and water for a specified period of time has proved to be effective in removing *C. difficile* from the hands of health care workers. To be clear, hand washing is defined as a scrub with chlorhexidine soap and water in an effort to remove skin oil (which harbors spores), followed by proper hand drying with a disposable paper towel. The time period for hand washing is at least 30 seconds, although the exact period of time required for optimal efficacy of this procedure is unclear. The Centers for Disease Control and Prevention (CDC) recommends substitution of alcohol-based hand rubs with hand washing with use of soap and water during outbreak situations. Alcohol-based products do remain highly effective against non–spore-forming organisms, are a vital part of increasing hand hygiene compliance in health care settings, and should not be abandoned for these reasons. It cannot be
overstated that compliance with proper hand-hygiene practices is one of the most effective measures for preventing the transmission of C. difficile as well as other organisms.

Hospital Cleaning Agents

As common detergents used in hospitals to clean patient rooms are not sporicidal, the intervention of using a 10% sodium hypochlorite solution has resulted in significant reductions in CDAD cases, as well as environmental spore burden. This same solution can be used to clean areas in the patient’s home to kill C. difficile spores and should be used to minimize the potential for reinfection.

One part of containing the spread of C. difficile during an outbreak is proper environmental disinfection. Replacing standard hospital cleaning agents, such as quaternary ammonium–based products, with 10% sodium hypochlorite solutions in the affected units (or universally) appears to be an effective intervention. Although manually prepared and diluted standard 1:10 sodium hypochlorite solutions are relatively inexpensive, they have the potential to be more noxious to environmental services employees, nursing staff, and patients, and require additional labor resources for daily preparation. Commercially available premixed hypochlorite-based cleaning agents, such as the disinfecting agent Dispatch (Caltech Industries, Inc., Midland, MI), are easier to prepare and administer to surfaces in a less noxious manner, but are significantly more expensive to purchase. In addition, their effect on the sporulation of C. difficile may be in question.

The Host

A variety of host-related variables influence the development of symptomatic CDAD, including immunity, age, exposure to antimicrobials, and possibly gastric acid suppression. Like environmental risk factors, these variables may provide opportunities for intervention to reduce the risk of C. difficile infection.

Immunity and Age

Patients in whom an immune response (circulation of antitoxin A immunoglobulin [Ig]G antibodies) cannot be properly mounted are more susceptible to recurrent CDAD. In fact, patients who develop serum antitoxin A IgG titers in response to colonization with C. difficile have been shown to be 48 times less likely to develop diarrhea than those who do not mount a response. As a corollary, older age has been associated with CDAD and is a plausible risk owing to the senescence of immunity. However, another group of authors noted that age was confounded by other variables. For instance, older patients tended to have more comorbid conditions that led to longer hospitalizations.

Antimicrobial Use

All antimicrobials (including certain chemotherapeutic agents) are viewed as risk factors for CDAD; however, some agents may pose greater risks than others. Proposed variables that may augment risk include extended durations of antimicrobial use, use of antimicrobials with antianaerobic activity, as well as exposure to agents lacking in vitro activity against the infecting strain of C. difficile. Prolonged exposure to antimicrobials further increases the risk for developing CDAD; thus, shorter durations of treatment should be used where data exist (e.g., urinary tract infections, ventilator-associated pneumonia, intraabdominal infections), and therapy should be stopped when the infection has been adequately treated or infection has been ruled out. Even single-dose administration of prophylactic antimicrobials has been implicated in inciting CDAD. It has been suggested that antimicrobials with activity against anaerobes may result in greater risks for CDAD than agents lacking anaerobic activity; however, this theory has not been supported by quality evidence. For example, antimicrobials with potent activity against anaerobes such as piperacillin-tazobactam have been suggested to be protective against CDAD or at least minimally offensive, whereas fluoroquinolones lacking activity against anaerobes (e.g., levofloxacin, ciprofloxacin) have been strongly implicated in well-conducted studies. A case-control study at our institution conducted over a 2-year period during the beginning of our outbreak attributed to BI/NAP1 evaluated risk factors for CDAD. We matched each consecutive symptomatic CDAD case patient with two control patients based on date of...
hospital admission, admission unit, age, and sex, with all other variables (e.g., days at risk, previous gastrointestinal surgery, exposure to gastric acid suppressants, presence of feeding tube, and severity of illness assessments using the Charlson Comorbidity Index and the Horn Index) being controlled for using multivariate analysis. The following risk factors (relative risk, p value) were identified as independent antimicrobial exposure risk factors for CDAD on multivariate analysis: cephalosporins (14, 0.007), macrolides (5.51, 0.035), vancomycin (4.18, 0.009), and fluoroquinolones (3.19, 0.006). Proton pump inhibitor use (2.89, 0.006) and the presence of a feeding tube (10.6, 0.002) were found to be nonantimicrobial risk factors for developing CDAD. Of interest, cephalosporins were associated with the greatest risk (relative risk 14, p<0.007), clindamycin was not identified as a risk factor (similar to the findings of others), most of our strains were clindamycin susceptible), and differences in risks between fluoroquinolones based on in vitro potency against anaerobes or by primary route of elimination (e.g., renal vs hepatobiliary-gastrointestinal) could not be distinguished.

Furthermore, an evaluation of comparative clinical studies (phases II–IV) of more than 21,000 patients, including hospitalized patients enrolled in the United States and Canada, did not reveal differences in CDAD between the antianaerobic fluoroquinolone moxifloxacin and comparators. A recently published double-blind, randomized, controlled trial evaluating the safety of moxifloxacin versus levofloxacin in hospitalized elderly patients with community-acquired pneumonia also revealed no differences in CDAD rates between moxifloxacin (1/195 patients [0.5%]) and levofloxacin (6/199 patients [3.0%]).

Finally, and more plausibly, exposure to antimicrobials that lack activity against C. difficile has been shown to be a risk factor for CDAD. This is thought to occur secondary to the selective survival advantage provided by the antimicrobial, resulting in intestinal overgrowth of C. difficile. Based on this, one of the few proven formulary interventions to curb CDAD rates in hospitals was accomplished by restricting clindamycin use during an outbreak of clindamycin-resistant C. difficile strains. Because clindamycin seems to have a unique, prolonged effect on intestinal flora, resulting in an extended susceptibility window for CDAD acquisition, perhaps the success of this formulary intervention cannot be extrapolated to other antimicrobials. The implications of BI/NAP1 being fluoroquinolone resistant may mean that the use of this entire class of antimicrobials should be reserved or perhaps restricted during outbreak settings. Indeed, because BI/NAP1 resistance is uniform to all fluoroquinolone class members tested, no advantage can be gained by using one preferentially over another. For many common respiratory tract infections, the abandonment of fluoroquinolone use seems impractical as it would only lead to the increased use of other C. difficile precipitants such as the cephalosporins.

Ultimately, evaluating risk factors for CDAD has been inherently difficult due to the numerous and complex relationships among variables. In fact, most studies have failed to adequately address important confounding variables, resulting in serious threats to the validity of their findings. Since the published critique of past CDAD risk factor ascertainment studies several studies have been presented or published that are better designed to assess risk. However, one of the chief difficulties in risk factor ascertainment studies for CDAD that remains is the fact that many patients have received multiple antimicrobials in the 6–8 weeks preceding development of CDAD, further complicating the ability to assign blame to a particular agent. Also, due to the retrospective nature of their study design, it is difficult to obtain a completely accurate outpatient antimicrobial history. And the more commonly used antimicrobials can be more commonly implicated in CDAD, as highlighted by the case of the fluoroquinolones. Thought of previously as low-to-moderate risk antimicrobials, these agents are now used with greater frequency in many geographic areas and have been more commonly identified as risk factors for CDAD. Thus, the issues related to assigning risks to antimicrobials for precipitating CDAD are complex. It is therefore difficult to strongly support a single unifying theory that describes an antimicrobial’s comparative risk for causing CDAD (e.g., possessing or lacking antianaerobic activity) based on the current published evidence is difficult. More research is needed to properly delineate the complex interrelationship between antimicrobial use and the other risk factors that contribute to CDAD.

Although practical considerations prevent us from knowing susceptibility data for C. difficile strains to a broad range of antimicrobials at our institutions, and whether or not antianaerobic activity deserves further attention, it is clear that
interventions directed toward optimizing antimicrobial use are beneficial for reducing CDAD rates. This was demonstrated by the findings from a recent systematic review on interventions to improve antibiotic prescribing practices among hospital inpatients. In accordance with these findings, it is imperative that antimicrobials be used in a more discriminating manner, as patients may develop life-threatening CDAD as an adverse effect of a practitioner’s treatment decisions.

Gastric Acid Suppression

Suppression of gastric acid can increase host susceptibility to infection and has been documented as a risk factor for a variety of infections that include travellers’ diarrhea, salmonellosis, cholera, as well as ventilator-associated pneumonia. One group of authors used cohort and case-control study designs to determine whether or not exposure to proton pump inhibitors was an independent risk factor for CDAD. Multivariate analyses revealed statistically significant adjusted odds ratios (95% confidence interval) of 2.1 (1.2–3.5) and 2.7 (1.4–5.2) in the two studies identifying proton pump inhibitor use as a risk factor for CDAD.

The use of gastric acid suppressants has also been associated with the development of community-acquired CDAD. Others have also implicated the use of proton pump inhibitors as an independent risk factor for CDAD, whereas one study did not find an association. In our institutional outbreak attributed to BI/NAP1, proton pump inhibitor exposure was determined to be an independent risk factor for CDAD after correcting for confounders. Future prospective studies of this association are warranted; however, given the current evidence, it seems logical to increase vigilance regarding the stewardship of proton pump inhibitor use.

Our Experience

The previous sections describe what has been learned about the epidemic strain of C. difficile known as BI/NAP1. In this section, various challenges we have faced related to the discovery and management of BI/NAP1 at our 600-bed community teaching hospital are discussed. Although some of the issues discussed may be common sense to the erudite reader, we were surprised by our observations in the clinic.

In 2002 as a part of our Antimicrobial Stewardship Program’s daily review of antimicrobial therapy, we began to notice an enormous variability in the treatment of CDAD along with the introduction of non–evidence-based practices in the treatment of CDAD at our institution (oral vancomycin plus oral metronidazole, extended durations of therapy beyond 10–14 days, “prophylaxis” with metronidazole for patients receiving antibiotics, donor stool transplantation, formulary requests for probiotics, cholestyramine use). Unaware of a simultaneous investigation by the CDC at other hospitals in the United States, we requested that our laboratory culture clinical isolates of C. difficile for the purposes of susceptibility testing by a notable expert (Dale Gerding, M.D., Hines VA Hospital, Hines, IL) in this field. The chief reason for doing this was that the previous outbreaks caused by J-type strains had been controlled by restricting clindamycin, the caveat being that the J-type strains were uniformly clindamycin resistant. To our disappointment, our isolates were clindamycin susceptible, thus removing a simple formulary change from our quiver of countermeasures; furthermore, the organisms tested were of a previously uncommon type. Serendipitously, we found ourselves in the midst of an outbreak due to BI/NAP1.

Combined efforts among the CDC, Dr. Gerding’s laboratory, and others established newly identified characteristics of this previously uncommon strain of C. difficile. We continued our antimicrobial stewardship efforts and worked with our colleagues in infection control, environmental services, and hospital administration to address environmental issues. Realizing that CDAD management guidelines had not been updated in nearly a decade, we collaborated with the departments of gastroenterology, surgery, pharmacy, and infectious diseases to establish evidence-based (where possible) treatment guidelines in order to address our current situation in the new era of BI/NAP1. We developed local guidelines in part because of the rash of non–evidence-based strategies being used. We reviewed the literature and consulted with experts in the field, which resulted in our final product (Figures 3 and 4). Through this process, we have corralled what we termed “the Wild West” approach to CDAD management, while reintroducing a more evidenced-based mentality. Subsequently, standardized order sets mimicking our treatment guidelines were incorporated into our computerized physician order entry system. Realizing that the treatment modalities for
refractory CDAD lacked double-blind, randomized, controlled trial data, we were careful not to exclude potentially beneficial options. However, as eluded to, we extinguished a variety of alleged “panaceas” for *C. difficile* that lacked evidence of effectiveness and presented potential harm to patients.

First, a regimen consisting of oral vancomycin along with oral metronidazole for the initial episodes of CDAD had become almost routine

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**Figure 3.** Treatment of first and second episodes of *Clostridium difficile*-associated disease. *Review drug interaction potential before adding rifampin to a patient's regimen.*
practice. We learned that the primary reason for prescribing both drugs was if clinicians thought the patient was not responding to one drug early in therapy (e.g., day 2), the second drug was added. Thus, our guidelines now recommend reevaluation of therapy at days 4–6 and note that diarrhea should decrease but not necessarily resolve within this time frame. We state that if symptoms do not improve or are worsening during therapy, then the practitioner should switch from oral metronidazole to oral vancomycin (not add a new agent to an already failing regimen). This is important because data suggest that the very drugs used to treat \textit{C. difficile} may also predispose patients to future episodes of CDAD.\textsuperscript{3} Thus, if the goal is to allow for the recovery of the protective commensal organisms in the gastrointestinal tract, the combination of the two drugs cannot be conducive to this goal.\textsuperscript{62}

Some authors recently described that patients treated for CDAD did not respond as well to metronidazole as first-line therapy,\textsuperscript{63} but quality evidence to support this is lacking.\textsuperscript{64, 65} Resistance to metronidazole and vancomycin among clinical isolates of \textit{C. difficile} (both outbreak and nonoutbreak strains) in the United States and elsewhere does not seem to be

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**Figure 4.** Treatment of third or more episodes of \textit{Clostridium difficile}-associated disease or severe cases of first and second episodes. *Review drug interaction potential before adding rifampin to a patient's regimen.*
Unfortunately, the literature is almost universally nonexistent. One possible explanation for the observations of poor response to metronidazole or vancomycin in the clinic is that patients are experiencing greater disease severity due to hypertoxin production and lasting disease due to increased sporulation of BI/NAP1.

Second, we received considerable pressure to add probiotic formulations to our hospital formulary for the management of CDAD. Thus, we conducted a MEDLINE search for studies that evaluated probiotic therapy of CDAD. We could find little if any quality evidence supporting their efficacy but did find unexpected evidence to support their harm, chiefly in the form of numerous reports of fungemias due to Saccharomyces boulardii and bacteremias due to Lactobacillus sp after probiotic administration to both immunocompetent and immunocompromised hosts.

A recent review of the literature emphasized the potential harm associated with S. boulardii. To this end, probiotics at this juncture are not recommended at our institution.

Third, we noted the increased use of anion-binding resins or adsorbents (cholestyramine, colestipol) at our institution. Although theoretically beneficial as binders of select C. difficile toxins, colestipol has been shown to be equivalent to placebo for its ability to affect the fecal excretion of toxins. Current evidence suggests that these drugs bind to a variety of other drugs, including vancomycin, in the gastrointestinal tract, thereby rendering known effective agents potentially ineffective. Based on the unproven efficacy of anion-binding resins and their potential to neutralize the efficacy of proven therapies, experts have recommended against their use.

Unfortunately, the literature is replete with numerous review articles recommending the use of anion-binding resins, without supportive clinical efficacy data. Experimental toxin-binding polymers such as tolevamer are in development and may be useful if proved effective.

Fourth, we found some practitioners using “prophylactic” regimens of either metronidazole or vancomycin in patients (without diarrhea and with no suspicion of CDAD) who were receiving antimicrobial therapy for the treatment of an underlying infection, reportedly in an effort to prevent a future episode of CDAD. This “prophylactic” approach had been gaining in popularity before the introduction of our guidelines. We know that exposing patients to antimicrobials (including oral vancomycin and metronidazole) increases the probability of infection with C. difficile, as well as future relapses in those with documented infection. We also know that the treatments (oral vancomycin and metronidazole) are not effective in eradicating C. difficile spores. Therefore, administering oral vancomycin or metronidazole for “prophylactic” purposes is illogical, non–evidence based, and potentially harmful in that it may increase the patient’s risk for CDAD.

Fifth, we noticed that oral vancomycin dosages varied widely for initial treatment of first episodes of CDAD and that treatment for extended durations beyond 10 days (often weeks) was becoming increasingly common. Our guidelines promote metronidazole as first-line therapy unless multiple episodes are documented, intolerance exists, or the patient is pregnant. When oral vancomycin is used, evidence dictates that 125 mg administered every 6 hours is equivalent to 500 mg every 6 hours in terms of efficacy, but the cost is significantly less. Higher doses of vancomycin (e.g., 2 g/day) administered to treat refractory CDAD have been shown to be effective in descriptive studies.

For refractory disease, multiple relapses, or patients with a poorly functioning gastrointestinal tract, we realize that high-quality evidence-based options are lacking. For patients with refractory disease (not responding at the day-4–6 evaluation point), we recommend switching from oral metronidazole to oral vancomycin (but to not use them in combination). Rifampin can be added if the patient continues not to respond, and surgical consultation is suggested if markers for severe disease are present (high white blood cell count, ascites, obstruction, toxic megacolon). We also reserve oral vancomycin at higher doses, such as 2 g/day, for patients with multiple relapses or those who fail to respond to therapy. Pulse-dosed or tapered vancomycin regimens are suggested for patients with multiple relapses, as previously described. In addition, although not supported by quality data but because there are no better solutions, intravenous metronidazole is recommended in patients with suspected toxic megacolon or ileus, with or without the use of intracolonic vancomycin.

Conclusion

A previously uncommon strain of C. difficile termed BI/NAP1 has been implicated as a cause of geographically diverse outbreaks of CDAD. Certain virulence characteristics may be responsible
for more severe clinical presentations and poor outcomes. Putative virulence factors (e.g., hypertoxin production, hypersporulation) possessed by a previously uncommon strain of *Clostridium difficile*, in conjunction with particular host and environmental factors, just may have resulted in the “perfect storm.” It is too simplistic to assume that a basic change in an antimicrobial formulae as a single intervention strategy will be successful in reducing CDAD rates where BI/NAP1 is endemic; policies that incorporate good antimicrobial stewardship along with infection control and environmental interventions are likely to be necessary to combat CDAD. The misuse of antimicrobials and the failure to comply with hand washing have increasingly dire consequences for both patients and health care workers. While awaiting updated national guidelines for the management of CDAD, we developed local guidelines to reestablish evidence-based treatment, where possible, and provide direction in the wake of BI/NAP1. Finally, the reasons for suboptimal infection control and antimicrobial use in modern times are similar: derisory resources both human and financial, apathy, and ignorance. It is therefore up to clinicians and administrators alike to work on all three of these elements that stand in the way of curbing the growing epidemic of CDAD.

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