The role of acute care surgery in the treatment of severe, complicated *Clostridium difficile*–associated disease

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Abstract: Clostridium difficile associated disease (CDAD) is the result of colonic bacterial overgrowth with this gram positive anaerobic organism and the production of toxins that typically induce diarrhea. Most patients with CDAD respond to treatment with oral metronidazole or vancomycin, but a subset of patients will develop a severe systemic illness, multiple organ failure, and death. There are no reliable combinations of clinical or laboratory findings that will distinguish patients who will respond to medical therapy and those who will progress to a more complicated state. Early surgical consultation should be considered in patients with ileus, severe abdominal pain, significant tenderness, immunosuppression, advanced age, high white blood cell or band counts, acute renal failure, mental status changes, or cardiopulmonary compromise. The standard operation for fulminant colitis is subtotal colectomy but the high mortality of the operation, and the long-term morbidity even in survivors combine to act as deterrents to early surgical consultation and operation. Novel operative approaches that preserve the colon and minimize operative morbidity may prove to remove the barriers to earlier surgical treatment for fulminant CDAD and improve outcomes.

Clostridium difficile is an anaerobic, spore-forming, gram-positive bacillus that is now the leading cause of nosocomial diarrhea in the United States. *C. difficile* colitis was initially identified in the 1970s and has since gained increasing notoriety owing to its associated high morbidity (30–80%) and mortality (4–10%).[1] The annual cost for the treatment related to hospitalizations for *C. difficile*–associated disease (CDAD) in the United States is approximately $3.7 billion.[2] *C. difficile* is associated with a $3,669.00 increase in estimated hospital costs per case and a 55% increase in length of stay.[3] The reported incidence of "fulminant" or "severe, complicated" CDAD, defined as CDAD with concomitant systemic toxicity and organ dysfunction, was 0% in 1990 and 3.2% in 2000.[4] In a study of US trends from 2000 to 2006, the incidence of CDAD in adults ranging in age from 18 years to 44 years increased from 1.3/10,000 to 2.4/10,000, while in those of ages 65 years to 84 years, CDAD increased from 22.4/10,000 to 49/10,000 and in those older than 85 years. CDAD nearly doubled from 52/10,000 to 112/10,000.[5] With the emergence of new more toxigenic strains of this bacteria, increased recognition/prevalence of CDAD, and high disease recurrence rates, there seems to be a growing need for more frequent and early surgical consultation and more effective and less morbid forms of surgical management.

A DISEASE OF BACTERIAL OVERGROWTH/TOXIN PRODUCTION

Pathophysiology

CDAD is acquired through the oral ingestion of *C. difficile* spores, which are resistant to gastric acidity and thus are able to germinate into the vegetative form in the small intestines. *C. difficile* colonizes the colon after the normal gut microflora is disrupted by antibiotic therapy or other host factors. In a study by Kyne et al.,[6] 31% of patients who received antibiotics in the hospital were shown to be colonized with *C. difficile*, and 56% of these patients developed symptomatic disease. With colonization and depletion of competitive flora, the *C. difficile* is free to overgrow and produce exotoxins, which induce injury, inflammation, and mucosal death. Most often, the consequences of toxin production are limited to the colon, resulting in the stereotypical diarrhea associated with this infection. In that small subset of patients with more severe disease, the consequences of the toxemia become systemic secondary to the cytokines and inflammatory mediators produced within the inflamed colon. It is rare, and not until late in the disease process that perforation caused by colonic ischemia or necrosis occurs. Our group believes that colonic necrosis/perforation occurs in the setting of nonocclusive mesenteric ischemia from gross volume depletion and/or high-dose vasopressor treatment or if a patient develops abdominal compartment syndrome secondary to colonic distention/inflammation, severe ileus, and third spacing of fluid.

The reason why only a subset of patients exposed to antibiotics become colonized, why only a fraction of these patients develop symptomatic disease, and why some patients experience more severe disease compared with others is largely unknown. Some authors suggest that differing humoral antibody responses to the toxins are largely responsible for both the development of infection/colitis and the varying severity of disease.[7] It has been reported that asymptomatic carriers have serum immunoglobulin G (IgG) antitoxin levels that are three times greater than those of patients with symptomatic disease. Patients with high serum IgG antibody titers during the first episode of CDAD are 48 times less likely to develop recurrent CDAD compared with those with lower antibody titers. The importance of the immune response in host defense gains further support from the recent report that the incidence of recurrent CDAD can be reduced by the administration of monoclonal antibodies to *C. difficile* toxins.[8–10]

The epidemiology of *C. difficile* has changed dramatically with widespread regional outbreaks involving more virulent and refractory strains (BI/NAP1/027). BI/NAP1/027 carries a deletion in the *tcdC* gene, which is a natural inhibitor of toxin production. This new toxigenic strain produces 15 to 20 times more toxin than do more commonly identified strains.[11] The exact contribution of this strain to the increasing incidence of fulminant CDAD has not yet been determined. At the University of Pittsburgh, however, these more severe strains account for most of all of the CDAD treated in the hospital (Scott Curry MD, personal communication, March 2012).

RISK FACTORS FOR INFECTION

Major risk factors for the development of CDAD are antibiotic exposure, hospitalization, and advanced age (Table 1). Recent antibiotic exposure is clearly the most important risk factor (relative risk, 5.9). The likelihood that *C. difficile* is the cause of antibiotic-related diarrhea increases with the severity of disease. Some antibiotics are notorious for *C. difficile* infections, that is, clindamycin, second- and third-generation cephalosporins (especially ceftriaxone), and fluoroquinolones.[12–15] It has also been proposed that the widespread use of fluoroquinolones contributed to the outbreak of BI/NAP1/027 in Canada and in other locations.[16–18] It is important to note, however, that antibiotic exposure is not an absolute prerequisite for the development of CDAD.

TABLE 1. Major Risk Factors for Development of CDAD

Antibiotics
Hospitalization
Long-term care facilities
Immunosuppression
Advanced age
Postoperative
Proton pump inhibitors
Elemental diets
Inflammatory bowel disease

A single dose of perioperative antibiotics can convert 20% of patients from *C. difficile* negative to positive by laboratory examination even in the total absence of symptomatic disease.[19] Canadian investigators found an increase from 0.7 cases of CDAD per 1,000 procedures in 2002 to 14.9 in 2005, coincident with the institution of routine prophylactic antibiotics for surgical procedures.[20]

Most *C. difficile* transmission occurs in the hospital. In one study, only 3% of the adults in the community were colonized with *C. difficile,* while 20% to 40% of hospitalized patients were colonized.[21,22] High colonization rates are also found in long-term care facilities and nursing homes. In these settings, spores can be found on environmental surfaces and remain viable for several years, emphasizing the need for rigorous infection control. The risk of *C. difficile* acquisition has also been strongly correlated with the length of stay in the hospital. The estimated incidence of colonization after less than 1 week of hospitalization is 1%, while after greater than a 4-week hospitalization, the incidence is approximately 50%.[15]

Advanced age also seems to be a significant risk factor, not only for infection with *C. difficile* but also for the severity of the colitis. Fulminant CDAD tends to affect the elderly with patients older than 65 years having a 20-fold higher risk of severe disease compared with younger patients.[15] Immunosuppression either in the setting of organ transplantation, treatment of malignancy, or human immunodeficiency virus has proven to be an additional major risk factor to the development of CDAD.[23,24] There is much evidence demonstrating the importance of the immune response in determining host susceptibility to infection with *C. difficile*.[25–27] The combination of a suppressed immune response, antibiotics, and hospitalization creates a perfect storm favoring CDAD. Other risk factors include underlying disease severity, gastrointestinal surgery, inflammatory bowel disease, nasogastric tubes, gastric acid suppression, elemental diets, uremia, burns, chronic obstructive pulmonary disease, cesarean delivery, antiperistaltic drugs, and, as expected, a previous episode of CDAD.

Recent studies have suggested that acid suppression with proton pump inhibitors has a better correlation with the increase incidence of *C. difficile* over antibiotic use.[28–30] It has been proposed that this finding is related to spores being resistant to acid exposure, while the vegetative form of *C. difficile* is killed by gastric acid exposure. With the use of proton pump inhibitors, the vegetative form is able to pass through the stomach and colonize the small and large intestine.

SIGNS/SYMPTOMS

The severity of symptoms from CDAD ranges from mild diarrhea to sepsis. The most common clinical presentation is diarrhea associated with history of antibiotic use (up to 12 weeks after the termination of antibiotics). Patients with diarrhea may have cramps, fever, and fecal leukocytes. Bowel movements are usually watery, with a characteristic foul smell. Fever occurs in 28%, leukocytosis in 50% (counts can approach $50 \times 10^9/\mu L$), and abdominal pain in 30% to 60% of patients. Hypoalbuminemia often occurs as a result of large protein losses and is a sign of severe disease. For most mild cases, diarrhea is usually the only symptom. However, there are rare occasions, especially in toxic patients with ileus, during which diarrhea may be absent.

DIAGNOSIS/WORKUP

The diagnosis of CDAD is based on a combination of clinical and laboratory findings: symptoms, almost always diarrhea, plus a stool test positive for *C. difficile* toxins or molecular evidence of toxigenic *C. difficile*. Visual or pathologic evidence of pseudomembranous colitis is also diagnostic. A careful history will usually confirm exposure to antibiotics; however, this is not absolutely necessary.

There are a number of laboratory tests that can be performed on diarrheal [unformed] stool, which in conjunction with clinical suspicion, can help make the diagnosis of CDAD. Formed stool should not be sent for testing because asymptomatic carriers and recovering victims will both give positive test results, which do not require treatment. In the setting of a clinical syndrome consistent with CDAD, medical treatment should not be delayed while awaiting the results of the diagnostic workup.[31]

The most useful laboratory tests are those in which the results are available within a day or two, that is, the cell culture cytotoxicity assay, polymerase chain reaction assay, or enzyme-linked immunoassay. Wren et al.[32] have critically reviewed the value of available diagnostic tests.

The use of polymerase chain reaction for the detection of *C. difficile* toxigenic genes is increasing in clinical laboratories. This test has the advantage of being rapid and highly sensitive and specific for toxigenic *C. difficile*.[33] Anaerobic stool culture is the criterion standard for diagnosis of CDAD. Stool cultures are sensitive but are not clinically useful for routine diagnosis because the isolation and identification of the suspect organism requires several days plus an additional period to determine whether the isolated strain is toxigenic.

Although colonoscopy/proctoscopy is able to identify pseudomembranes, which are pathognomonic of CDAD, this diagnostic method is less sensitive compared with stool toxin assays simply because pseudomembranes are not always present; the false-negative rate quoted in larger series is 10% to 25%.[24] Pseudomembranes can involve the entire colon, although they can be unpredictably segmental in nature. Endoscopy may be of maximum benefit for patients in whom the clinical suspicion of CDAD is high, yet laboratory test results continue to be negative. In this scenario, endoscopy provides direct inspection of the mucosa as well as tissue and stool samples for toxin assay and culture.

Computed tomographic (CT) scan, with or without contrast, has been found to be a useful adjunct for evaluation of the colon in a patient with suspected CDAD. It is much less sensitive than stool toxin assays, and the changes seen are rarely diagnostic. The sensitivity and specificity of CT scan to identify colonic abnormalities in these patients is 52% to 85% and 48% to 93%, respectively.[34] Fulminant colitis is most often marked by in CT scan evidence of colonic thickening, pericolonic stranding, and the "accordion sign" (oral contrast material with high attenuation in the colonic lumen alternating with an inflamed mucosa with low attenuation). A "double-halo sign" or "target sign" is often seen with intravenous contrast representing varying degrees of attenuation of the mucosa secondary to hyperemia and submucosal inflammation). Most severe CDAD will show changes throughout the entire colon (pancolitis) and moderate quantities of ascitic fluid (Fig. 1). We recommend surgical consultant when these radiographic changes are seen.

GENERAL MANAGEMENT

Infection control measures are extremely important both to prevent disease and to limit spread of the bacterium. In all cases, standard infection control precautions must be instituted. For CDAD, this includes room isolation and contact precautions,

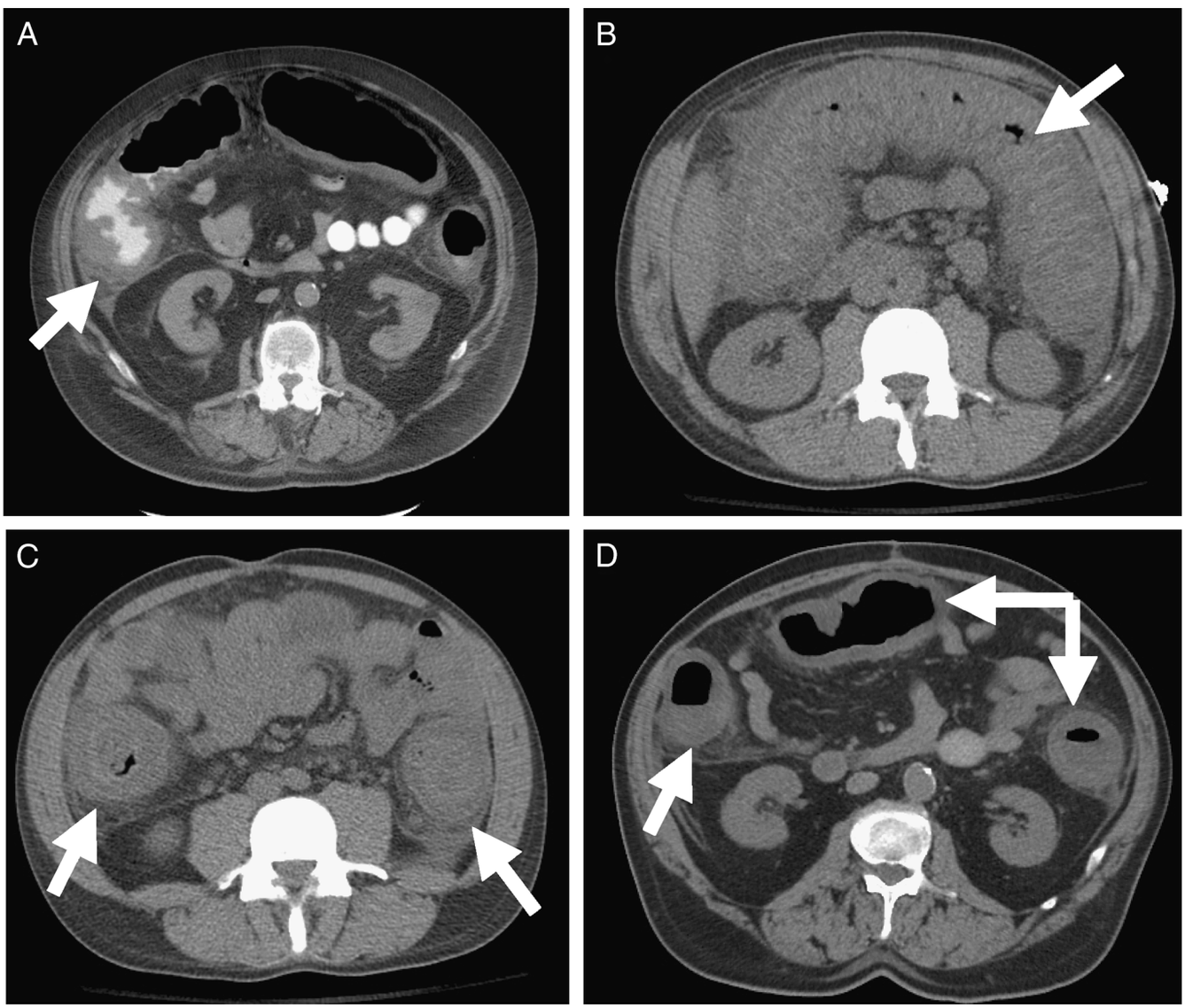

Figure 1. CT scan findings of pancolitis. CT scan findings of CDAD are nonspecific but most often include pancolitis with or without ascites. Findings include colonic wall thickening, pericolonic edema and pericolonic fat stranding. *A,* Colitis involving the ascending, transverse, and descending colon is demonstrated in this CT image. The *arrow* demonstrates colonic wall thickening, pericolonic edema, and fat stranding. Enteral contrast is seen within the ascending colon, highlighting the thickened colonic wall. *B,* Thickening of the colonic wall with enhancing mucosa is demonstrated in the transverse colon (highlighted by the *arrow*). This thickening gives a classic ''accordion'' sign. *C* and *D*, The *arrows* point out thickening of the colon, as well as pericolonic edema and fat stranding.

use of barrier precautions (gown and gloves), mechanical hand washing with soap and water (as spores are not killed by hand sanitizer preparations), and environmental cleaning with a bleach-based cleanser.[35] Prudent antibiotic use and antibiotic stewardship programs are likely useful to limit disease or recurrence.

Antiperistaltic agents and narcotics are thought to contribute to ileus and exacerbation of the severity of disease and should be avoided in medical management. The basic tenants in the care of patients with critical illness care should be maintained, such as provision of fluid and electrolyte replacement. Fecal management systems may be necessary for the comfort of bedridden patients.

MEDICAL MANAGEMENT

If possible, the antibiotics previously used for the treatment of systemic infections should be discontinued, a goal which cannot always be accomplished because of persistent systemic infections. In fact, there are no consensus recommendations on CDAD management in such patients. Our recommendation for antibiotic management in the setting of CDAD with concurrent pathologic finding that requires antimicrobials is to stop the antibiotic that was being used when CDAD developed and avoid the use of antibiotics that have been most associated with the development of CDAD (clindamycin, cephalosporins, and fluoroquinolones). The antibiotic that is chosen to treat the other ongoing disease should be used in addition to CDAD treatment.

The recommended medications for CDAD (metronidazole or vancomycin) must achieve therapeutic concentrations within the lumen of the colon to be effective. For metronidazole therapy, delivery can be via enteral or intravenous routes. Intravenously administered metronidazole can achieve therapeutic concentrations in the colon via biliary excretion into the gastrointestinal tract. It is important to consider that neither oral nor parenteral metronidazole reaches therapeutic concentrations in normal, nondiarrheal stool; thus continuing its administration more than 14 days for patients whose diarrhea resolves has no therapeutic value. Vancomycin must be delivered enterally to achieve therapeutic levels in the colon. Vancomycin by the intravenous route is totally ineffective against CDAD because it does not reach the intestinal lumen. However, standard oral dosing of vancomycin achieves a minimum inhibitory concentration in the stool both in the setting of diarrhea or nondiarrheal bowel movements.[36,37]

The two drugs are generally considered equally effective for mild/moderate disease, but metronidazole is less expensive.[38,39] Mild/moderate disease in adults usually responds to oral metronidazole 500 mg 3 times a day for 10 days to 14 days. Severe disease (defined by the Infectious Disease Society of America as CDAD with a white blood cell count greater than $15 \times 10^9/\mu L$ or a creatinine level increased 50% over baseline [without hypotension, shock, or ileus]) is better treated with vancomycin 125 mg 4 times a day for 10 days to 14 days (Table 2).[35,40]

Fidaxomicin is a macrocyclic antibiotic that recently was approved for use in CDAD. A Phase III trial revealed that fidaxomicin was noninferior to vancomycin for clinical cure rate but was more effective than vancomycin in reducing disease recurrence (15.4% vs. 25.3%).[41] However, fidaxomicin was not superior to vancomycin in reducing recurrence for patients infected with the more virulent BI/NAP1/027 strain. The long-term role for fidaxomicin in the treatment of CDAD has not yet been determined, although it does not seem to be preferred as first-line therapy.

Some patients with severe CDAD do not have diarrhea but instead present with ileus and may progress to toxic megacolon. We recommend surgical consultation for any patient with CDAD and ileus (or hypotension). For patients with ileus, vancomycin enemas have been successfully used as a means to supply the needed drugs to the colonic lumen. Colonic vancomycin enemas should be delivered using a dose and enema volume that will reach the ascending colon (500–1,000 mL). Smaller enema volumes as are unlikely to reflux past the sigmoid colon. To this end, several small series have described the successful use of a long fenestrated tube passed proximally via the colonoscope. Such tubes can both decompress the dilated inflamed colon and infuse vancomycin into the lumen.[42,43] Colonic perforation is an obvious concern with the use of colonoscopy and indwelling long rectal tubes in this setting.

Additional antibiotics in place of metronidazole, vancomycin, or fidaxomicin have been shown to be effective but are generally reserved for treatment of nonresponders, and experience is relatively limited. Table 3 lists some of the therapies reported to be of benefit in the treatment of CDAD.

Recurrent disease after seemingly successful medical management is common in CDAD and occurs in 15% to 35% of patients within 3 months after initial treatment.[44] Vancomycin

TABLE 2. Classification Schema for *Clostridium difficile* Infection and Recommended Antibiotic Treatment Strategy as Outlined in Society for Healthcare Epidemiology of America/Infectious Diseases Society of America Treatment Guidelines[35]

Category	Criteria	Treatment	Strength/Quality of Evidence
Mild or moderate	Diarrhea	Metronidazole 500 mg per os three times a day	A-I
Severe	WBC $>15 \times 10^9/\mu L$ or creatinine level increased 1.5-fold greater than baseline level	Vancomycin 125 mg per os four times a day	B-I
Severe, complicated	Ileus, "megacolon," hypotension, or shock	Metronidazole 500 mg intravenously administered three times a day + vancomycin 500 mg PO 4 times a day (+ vancomycin enemas in ileus)	C-III

This scoring system is not yet validated.

therapy is superior to metronidazole with respect to the recurrence rate, yet rates continue to approach 25%.[41] Recurrent disease may be caused by reinfection or to germination of spores that were not previously killed given the fact that metronidazole and vancomycin are able to kill the vegetative forms of *C. difficile* but have no effect on the spores that can later germinate when treatment is discontinued. One study, however, demonstrated that more than 50% of the relapses are due to infection with a different strain of *C. difficile* suggesting that spores may not be the only reason for recurrent disease.[45]

First recurrences are usually treated in a similar fashion to initial episodes, and drug choice is based on disease severity. Subsequent recurrences should be treated with a course of vancomycin with a taper of therapy over time (usually 7 weeks). This choice of vancomycin rests in part on the ability of oral vancomycin to achieve effective concentrations in nondiarrheal stool. In addition, the taper dosing strategy may promote spores to germinate and subsequently be killed by vancomycin. The use of fidaxomicin in this setting has not yet been determined.

The best treatment of refractory severe CDAD has not been definitively established. A variety of innovative biotherapeutic approaches have been tried, and some successes have been claimed. Most have been used in combination with oral metronidazole or vancomycin and represent attempts to more rapidly restore an alternative or more normal colonic flora. Among these are therapeutic enemas containing microbial competitors—such as nontoxigenic *C. difficile*, fecal bacteriotherapy, or probiotics. Fecal bacteriotherapy (fecal transplants) through the instillation of stool via a nasogastric tube or colonoscopically has shown some promising results in a small series of patients with critical illness but has not gained mass appeal because of aesthetic concerns and questions of donor selection.[46,47] Despite these limitations, this therapy might well prove useful, particularly for patients with multiple recurrences.

A meta-analysis performed by McFarland[48,49] on the use of probiotics reported a protective benefit of both *Lactobacillus* and *Saccharomyces boulardii*; only *S. boulardii*, however, was effective in preventing recurrent infections. One concern with the use of probiotic agents is that there have been some cases of *Saccharomyces cerevisiae* fungemia for patients that were treated with *S. boulardii* because the preparations were contaminated with *S. cerevisiae*. These products, consequently, should not be used in immunocompromised patients.[50]

Decreased serum antibody levels against *C. difficile* toxin have been found in patients with recurrent disease. Immune-based therapies, thus, hold promise for the future,[9] although at this point data only suggests benefit to decrease the rate of recurrences and not yet in the treatment of severe or fulminant disease. Immunity likely plays an important role in prevention of recurrent disease. Vaccines composed of formalin-inactivated toxins elicit good immune responses in animals. In Phase I human clinical trials, the vaccine has been shown to induce a significant immune response. In one recent report, three patients with multiple recurrences despite vancomycin treatment were administered this new vaccine, and two of three individuals had increases in IgG to toxin A and B, and all three patients were able to discontinue the oral vancomycin without evidence to date of recurrent disease.[51]

Additional immune-based strategies have included treatment with pooled intravenously administered gamma globulin that contains IgG against toxin A that has been demonstrated to help in the resolution of recurrent and refractory CDAD.[52] *C. difficile* toxin monoclonal antibodies have recently been shown to reduce the recurrence rate of CDAD.[9] No trials are yet complete for the use of passive administration of antibodies for the adjunctive treatment of severe CDAD or its prevention.

TABLE 3. Treatment Regimens in the Management of CDAD

Antibiotics
Commonly used or Food and Drug Administration–approved
Metronidazole
Enteral vancomycin
Enteral fidaxomicin
Adjunctive antibiotics
Bacitracin
Fusidic acid
Nitazoxanide
Rifaximin
Teicoplanin
Tigecycline
Toxin binding agents*
Cholestyramine
Tolevamer
Immunotherapy
Vaccines
Intravenously administered immunoglobulin
Monoclonal antibodies
Fecal bacteriotherapy
Probiotics†
S. boulardii
Lactobacillus species

*Toxin-binding agents should be used with caution because they may bind oral vancomycin and other medications.

†The use of probiotics has been associated with bacteremia or fungemia in immunocompromised patients or patients with critical illness.

COLECTOMY FOR SEVERE, COMPLICATED CDAD

The therapeutic guidelines require amplification when patients do not respond or deteriorate during treatment. In any patient with severe disease, early surgical consultation is required so that concurrent medical/surgical treatment planning can proceed for the unusual case in which operative intervention will be required. Patients with severe CDAD should also be considered for CT scanning of the abdomen/pelvis. Most of the patients with severe disease will not require surgical therapy; however, early surgical consultation helps to identify patients failing medical therapy or progressing to severe, complicated disease. Data reviewed in several series suggest that earlier colectomy (time from presentation to surgery) was associated with a significantly decreased mortality.[24,53–55] In an analysis of the literature dating from 1989 to 2009, Butala et al.[56] concluded that earlier diagnosis and treatment with subtotal colectomy and end ileostomy is critical in reducing mortality associated with fulminant CDAD.

TABLE 4. Indications for Surgical Consultation in Patients With Known or Suspected CDAD

Ileus/significant abdominal distention
Admission to intensive care unit
Hypotension (with or without vasopressors)
Mental status changes
WBC counts $\geq 35 \times 10^9/\mu L$
Serum lactate levels ≥ 2.2 mmol/L
Any evidence of end-organ failure
Age ≥ 80 years with severe CDAD criteria
Immunosuppression with severe CDAD criteria

Strength/quality of evidence, B-III.

Surgical treatment has been demonstrated to improve outcomes in severe, complicated CDAD, defined broadly as patients with CDAD admitted to intensive care units with organ failure or the need for vasoactive agents or ventilatory assistance.[23,55,57,58] As mentioned, a shorter interval from presentation to colectomy favors survival in many series, but in practice, the proper timing of operative intervention and the extent of the operation has not been settled. Segmental colectomy has been used in the past, with margins of resection based on the gross appearance of the colon at operation. Although partial colectomy has been successful, several studies suggest that the outcomes are inferior to subtotal colectomy.[59,60] Subtotal colectomy (sparing the rectum) and end ileostomy, the standard treatment of severe complicated (fulminant) disease, carries considerable morbidity and mortality. Concerns about the complications of colectomy, however, can lead to excessive delay in obtaining a surgical consultation, leading to an even less favorable outcome.

PROGNOSTIC FACTORS

A major challenge in the management of patients has been the inability to successfully predict which patients will respond to standard therapy and which patients will not. Dudukgian et al.[61] identified increased mortality for patients with preexisting conditions (renal/pulmonary disease, higher American Society of Anesthesiologists class, and the use of steroids) or certain clinical findings (lower diastolic pressure, higher Acute Physiology and Chronic Health Evaluation II [APACHE II] score, evidence of toxic megacolon, higher white blood cell (WBC) count, and clinical signs of sepsis and organ dysfunction).[40] They also found that increased length of hospital stay preceding the diagnosis of CDAD had a negative impact on survival. Others have confirmed that combinations of factors, including age, laboratory abnormalities (high WBC count, elevated band counts, increased lactate levels, decreased albumin levels), and signs of clinical deterioration (need for mechanical ventilation, vasopressors, renal failure, or mental status changes) are negative prognostic findings.[24] A major shortcoming of current prognostic strategies is that the presence of these factors defines fulminant disease in which the benefit of further treatment strategies (most notably surgical colectomy) becomes limited.

A number of severity scoring systems for CDAD have been developed to help predict mortality. Prognostic criteria have included advanced age, altered mental status, abdominal pain or distention, leukocytosis ($>20 \times 10^9/\mu L$) or leucopenia ($<1.5 \times 10^9/\mu L$) or greater than 10% band count, hypoalbuminemia (<2.5 g/dL), ascites or colitis documented by imaging, hypotension (mean arterial pressure, <65 mm Hg), fever (>101°F), tachycardia (>110 beats/min), presence of comorbid diseases, immunosuppression, and admission to intensive care unit.[40,62–65] Lower survival rates with fulminant CDAD are also associated with multisystem organ failure, higher APACHE II and III scores.[58,60] On critical review, all proposed severity scoring systems generally have poor positive predictive values, have excellent negative predictive values, and have been unable to predict the need for surgical intervention. Criteria using frequency or volume of bowel movements do not take into account of the common appearance of ileus in the most severely ill.

Prognostic Factors That Indicate the Need for Surgical Management

One of the greatest challenges of disease management has been determining the appropriate timing of surgical treatment of patients with severe complicated CDAD. There is no obvious answer to this dilemma. If traditional signs and symptoms of fulminant colitis or past definitions of "toxic megacolon" are relied on to initiate surgical consultation or management, poor outcomes will result. Once hypotension develops, the mortality significantly increases, and the patient may be unresponsive to vasopressor support.[66] Fulminant colitis has been somewhat subjectively characterized but has been

TABLE 5. Indications for Operative Management in Patients With CDAD (Strength/Quality of Evidence, B-II)

A diagnosis of *Clostridium difficile* colitis as determined by one of the following:
1. Positive toxin assay result
2. Endoscopic findings
3. CT scan findings consistent with *C. difficile* colitis (pancolitis with or without ascites)

Plus any one of the following criteria:
1. Peritonitis
2. Perforation
3. Worsening abdominal distention/pain
4. Sepsis
5. Intubation
6. Vasopressor requirement
7. Mental status changes
8. Unexplained clinical deterioration
9. Renal failure
10. Lactate level > 5 mmol/L
11. WBC count $\geq 50 \times 10^9/\mu L$
12. Abdominal compartment syndrome
13. Failure to improve with standard therapy within 5 d as determined by resolving symptoms and physical examination, resolving WBC per band count

defined by others as colitis complicated by perforation, severe ileus, toxic megacolon, vasopressor requirement, or evidence of organ failure. Patients with severe complicated CDAD typically demonstrate systemic toxicity with fever, hypotension, tachycardia, and impressive leukocytosis. Diarrhea may be present or may have subsided to be followed by paralytic ileus and colonic dysmotility often referred to as *toxic megacolon*. Toxic megacolon is itself an encompassing and vague term for colitis that combines massive dilation of the colon with fulminant systemic signs, and we discourage the use of this term in reference to CDAD. However, the literature has reported that toxic megacolon as a consequence of *C. difficile* is present in 0.4% to 3% of patients with CDAD with an associated mortality of 38% to 80%.[67]

Independent risk factors for mortality for patients undergoing colectomy for CDAD that have been consistently found among multiple studies include the development of shock, as determined by the need for vasopressors and increased lactate (≥5 mmol/L); mental status changes; and the development of end-organ failure. This includes the need for preoperative intubation and ventilation or renal failure.[23,24,54,55,57,68,69] Other recurring risk factors for mortality in this group includes advanced age, very high WBC counts (>50 $\times$ 10^9/μL), and immunosuppression.

We hypothesize that mortality from colectomy has been so high because clinicians await the development of signs of cardiopulmonary compromise or organ failure as signs of failure of medical therapy and as indications for surgery. These indeed are indications for urgent surgical therapy. However, to improve outcomes and patient survival from CDAD, the indications for surgical consultation/therapy should be expanded and be made more inclusive. Based on prognostic factors shown across multiple studies, we advocate a more inclusive strategy to "upstage" disease as severe, complicated and as indications for surgical consultation (Table 4). More specifically, recommendations for operative management supported by data include perforation, vasopressor requirement, clinical signs of sepsis and organ dysfunction (renal and pulmonary), mental status changes, WBC count 50$\times$ 10^9/μL or greater, lactate ≥5 mmol/L, or failure to improve on medical therapy after 5 days (Table 5). Other general indications include unexplained clinical deterioration or worsening clinical examination or status.

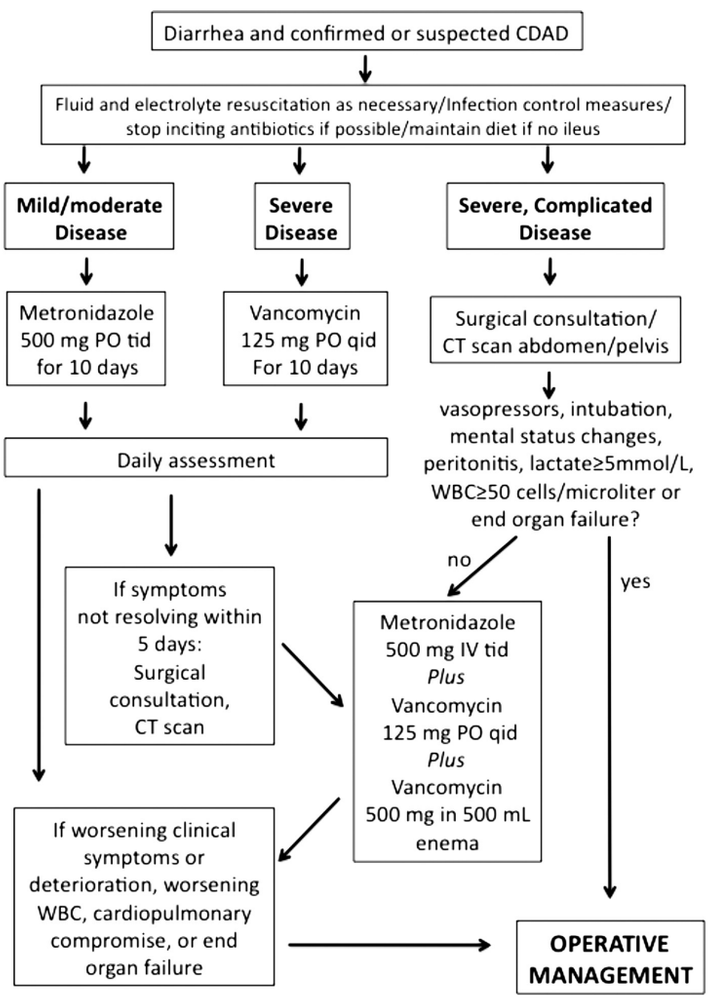

Figure 2. Management strategy for patients with CDAD.

FUTURE SURGICAL DIRECTIONS/ALTERNATIVE TO COLECTOMY

Because CDAD is in essence a mucosal disease, which rarely produces colonic necrosis/perforation, there is no a priori reason to remove the colon except to eliminate accumulated toxins along with the source of toxin production. Based on the experiences of others and our understanding of the pathogenesis of the disease, we have embraced an approach that does not involve colectomy.[70,71] Our approach to patients with fulminant CDAD who meet the criteria outlined in Table 5 has been to eliminate the toxic contents of the colon and reduce the load of *C. difficile* organisms. First, we divert the enteric stream, thereby by eliminating the inflow of microbial nutrients into the colon. Second, the colon is mechanically cleansed by the infusion of large volumes into the lumen and enabling evacuation. Third, a microbicidal concentration of vancomycin is flushed directly into the colon. These three aims can be accomplished at a single operation via a minimally invasive approach, thereby reducing operative morbidity.

In practice, a loop ileostomy is performed through a laparoscope; if this is not technically feasible, laparotomy can be performed. This approach permits inspection of the colon to be sure no other pathologic processes, including transmural necrosis or perforation, are present. The colon is then laved via the efferent limb of the ileostomy with 8 liters of warm polyethylene glycol (PEG) 3350/balanced electrolyte solution, and a catheter is left in the efferent limb of the ileostomy to deliver vancomycin into the colon in an antegrade fashion (500 mg every 8 hours) for 10 days. Simultaneously, physiologic support and continuing systemic metronidazole administration is continued until clinical responses are satisfactory.

Our preliminary results in 42 patients were promising, demonstrating significantly decreased mortality compared with our traditional management strategy for patients with similar severity of illness as determined by comparable APACHE II scores.[70] However, this therapy has not yet gained widespread use, and its validation outside our institution remains to be proven.

This approach is based not only on the pathophysiology of the disease process, but it also builds on anecdotal experiences. Saylor et al.[72] described the successful use of a diverting ileostomy in a patient in 1976. Additional isolated reports have suggested benefit from fecal diversion. Turnbull "blowhole"

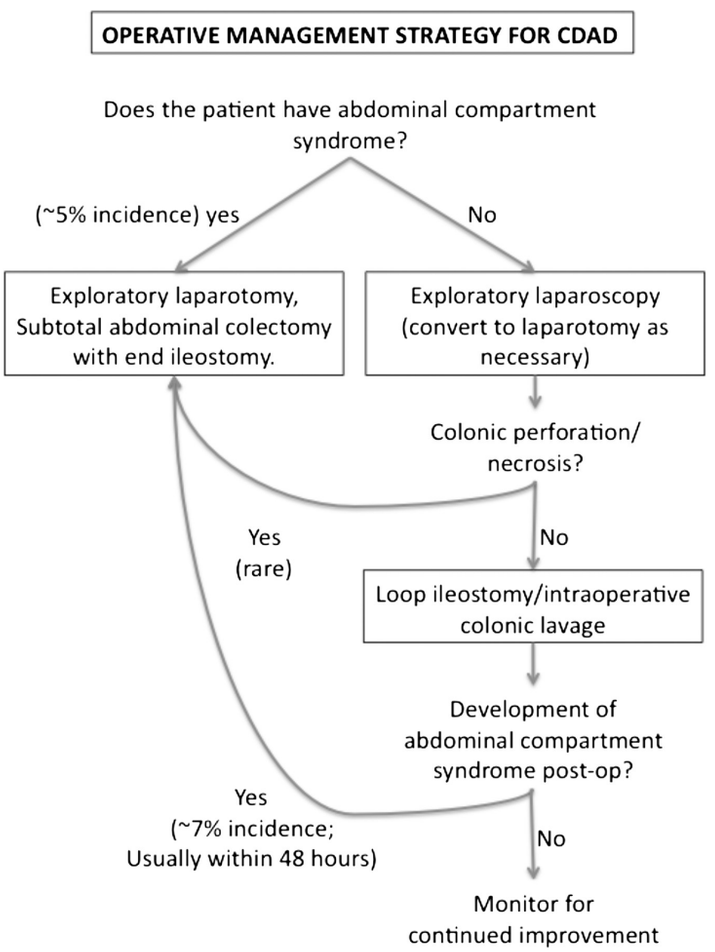

Figure 3. Operative management strategy for patients with CDAD.

colostomy for toxic megacolon in ulcerative colitis had been used as an effective strategy.[73,74] Liacouras and Piccoli[75] reported the successful use of whole bowel irrigation as an adjunct in the treatment of two pediatric patients with chronic, relapsing CDAD who had failed all other medical regimens. To reiterate, CDAD does not usually involve irreversible and compromised integrity of the colon requiring colectomy for source control. This operative approach spares the colon, which generally recovers once the infection has been eliminated. Reconstruction of the gastrointestinal tract, thereafter, only requires closure of the loop ileostomy.

The surgical insult of the operation is significantly lower than that of a colectomy. The availability of a less morbid operation should allow clinicians to consider operative intervention before the development of life-threatening circulatory and organ failure. The operation does not preclude subsequent total abdominal colectomy if the patient's condition does not improve. Our group has currently treated more than 70 patients, and we have seen 5 patients (approximately 7%) managed in this way develop abdominal compartment syndrome in the postoperative period. Two patients were managed with colectomy, and three were managed with decompressive laparotomy. Although in our experience we have managed patients with preoperative or postoperative abdominal compartment syndrome using loop ileostomy and washout with a decompressive laparotomy, followed by subsequent closure of the abdomen, we now advocate total abdominal colectomy in this setting, which has the advantage of a single stage operation and definitive management. Rigorous study and future trials will determine the adequacy of this procedure. Our current protocol for the treatment of patients with CDAD is outlined in Figure 2, and our operative approach is outlined in Figure 3.

CONCLUSION

CDAD is increasing in prevalence and suspicion of disease should prompt diagnostic testing and therapy based on this with initiation of medical therapy empirically if clinical suspicion is high enough. Most patients respond to medical therapy; however, the development of fulminant colitis warrants a proactive approach. Total abdominal colectomy and end ileostomy for CDAD has typically been reserved as a salvage procedure for patients late in the spectrum of their disease course and is associated with improved, yet high mortality. We propose an approach to consider earlier surgical consultation in the care of these patients as well as operative therapy earlier in the course of the disease for patients with severe complicated colitis. Although this recommended approach of earlier operation is applicable to total colectomy, we currently embrace an operative approach that serves as an alternative to colectomy in the treatment of these patients with severe disease. Further investigations that confirm the validity of this novel treatment strategy are warranted.

AUTHORSHIP

All authors contributed equally to this article. E.H.C., A.B.P., R.L.S., B.S.Z. participated in the literature search, hypothesis, data interpretation, writing of the article, and preparation of the figures.

DISCLOSURE

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