

Practice guidelines

Guidelines for the Diagnosis and Management of *Clostridium difficile*-Associated Diarrhea and Colitis

Robert Fekety, M.D.

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines are also approved by the governing boards of American College of Gastroenterology and Practice Parameters Committee. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time. The following guidelines are intended for adults and not for pediatric patients.

INTRODUCTION

Antibiotic-associated diarrhea and colitis are important and increasingly frequent complications of antibiotic therapy. While these occur most often in hospitals and nursing homes, they also occur in the community. Antibiotic-associated diarrhea is even more common; it is caused by *Clos-*

tridium difficile in only 15–20% of cases, and is of unknown cause in most of the remaining cases (1–3). The type of antibiotic-associated diarrhea that is *not* caused by *C. difficile* is relatively mild, self-limited, unassociated with intestinal lesions, is treatable with nonspecific supportive measures and by discontinuation of antibiotics, and is also referred to by a variety of terms such as simple, benign, or enigmatic antibiotic-associated diarrhea. In contrast, *C. difficile* associated diarrhea is usually associated with colitis caused by the combined effects of toxins A and B produced by *C. difficile* within the intestinal lumen and is a serious and potentially life-threatening disease. *C. difficile*, a spore-forming obligate anaerobic bacillus, is a component of the normal fecal flora of many infants, and about 5% of healthy adults; it may be found in the stools of 10% or more of hospitalized adults without diarrhea who have received antibiotics or cancer chemotherapeutic agents. *C. difficile* causes a spectrum of diarrheal syndromes that vary widely in severity and merge with one another; they are also commonly referred to by a variety of names, including *C. difficile* diarrhea, *C. difficile* colitis, antibiotic-associated *C. difficile* colitis, and pseudomembranous colitis. Unless specified otherwise, the general term “*C. difficile* diarrhea” will be used herein to refer to the entire spectrum of the diarrheal diseases caused by this organism. The diarrheal illness caused by *C. difficile* may and often does closely resemble the more frequent benign or simple antibiotic diarrhea. Patients with antibiotic-associated diarrhea in which *C. difficile* cannot be incriminated, which is true about 80% of the time, are assumed to have the simple or benign diarrhea of unknown cause.

C. difficile diarrhea, colitis without pseudomembranes, and pseudomembranous colitis are toxin-mediated mucosal inflammatory processes that are usually characterized by the presence of grossly or microscopically visible pseudomembranes consisting of nodules or large plaques containing leukocytes, fibrin, mucus, and epithelial cells loosely adherent to the surface of the underlying inflamed and necrotic mucosa. Almost all cases of antibiotic-associated colitis or pseudomembranous colitis are caused by both toxin A and

B producing strains of *C. difficile*. Most patients with *C. difficile* diarrhea can be found to have gross and/or microscopic colitis with or without pseudomembranes if they undergo a workup that includes colonoscopy with biopsies. When pseudomembranes are not evident in patients with *C. difficile* diarrhea who have undergone colonoscopy, the diarrheal process may have resulted from a purely secretory diarrhea without colonic inflammation. Because, for a variety of reasons, many if not most patients with antibiotic-associated diarrhea do not undergo endoscopy and biopsy, the general term “*C. difficile* diarrhea” is used more and more often when one of more laboratory tests for *C. difficile* are positive and the organism is considered to be the cause of the diarrhea, and it is not certain whether or not colitis and/or pseudomembranes are present. *C. difficile* diarrhea with colitis and pseudomembranes can lead to toxic dilation and/or perforation of the colon, dehydration, hypovolemia, shock, and death. Although pseudomembranous colitis was well-recognized in the preantibiotic era (and was thought to be caused by staphylococci), it is now uncommon to diagnose it in a patient who has not received antibiotics and in whom *C. difficile* cannot be implicated. As many as 20% of patients with *C. difficile* diarrhea do not develop symptoms until as long as 6–8 weeks after discontinuation of antibiotic therapy. In addition, patients have developed *C. difficile* diarrhea after the use of cancer chemotherapeutic agents, many of which have significant *in vitro* antibacterial activity (4–7).

PATHOPHYSIOLOGY OF *C. DIFFICILE* DIARRHEA

C. difficile diarrhea is caused primarily by the elaboration within the intestinal lumen of both toxin A and toxin B produced by *C. difficile* during its multiplication. These toxins bind to the colonic mucosa and then exert their damaging effects upon it. Most toxigenic isolates produce both toxins, but depending on whether they are obtained from infants, healthy adults, the environment, or persons with antibiotic-associated diarrhea, about 5 to 25% of isolates of *C. difficile* produce neither toxin A nor B, and do not cause colitis or diarrhea (5, 6, 8). Toxin A is a 308-kDa enterotoxin capable of causing extensive mucosal damage in experimental animals; it is cytotoxic for certain cell lines in culture, a chemoattractant for neutrophils, and an activator of macrophages and mast cells, causing them to produce various inflammatory mediators (8). Toxin A causes actin disaggregation and intracellular calcium release, and also appears to damage neurons (3–6). Toxin B is a 270-kDa cytotoxin that causes depolymerization of filamentous actin. Toxin B was first detected by virtue of its potent cytopathic effects in cell culture monolayers, but because it was not cytotoxic for the colonic mucosa of various animal species it was originally considered of little importance in causing colitis in humans. Recent evidence indicates toxin B disrupts the actin cytoskeleton, and is also a necrotizing enterotoxin 10 times more potent than toxin A in causing

damage to human colonic mucosa in cell cultures (9). It seems probable that both toxins are important in causing diarrheal disease in humans. *C. difficile* rarely damages the colon of patients by direct invasion, although it can occasionally do so (10), and it should be emphasized that the diarrhea the organism produces is caused by the effects of toxins that are produced within the intestinal lumen and adhere to the mucosal surface (3–6).

EPIDEMIOLOGY OF *C. DIFFICILE* DIARRHEA

The frequency and incidence of *C. difficile* diarrhea varies widely not only geographically but within different institutions in the same area, and depends on patterns of antimicrobial use, on antimicrobial resistance patterns of the prevalent *C. difficile* isolates, on epidemiologic factors favoring transmission of the organism, on patients' risk factors, on clinicians index of suspicion, and especially on the frequency with which endoscopy and/or various laboratory tests for the presence of toxins A or B in stools are performed on patients with antibiotic-associated diarrhea (4–6, 8, 11). Ironically, as the frequency of postoperative wound infections has declined over the past few decades, in no small measure because of the skill of surgeons and their appropriate use of short-course perioperative antibiotic prophylaxis in high-risk patients, the frequency of *C. difficile* diarrhea has markedly increased in hospitals in the United States, especially in the elderly (12). Almost every popular antimicrobial has been implicated in the causation of *C. difficile* diarrhea, but ampicillin and other penicillin derivatives, cephalosporins and clindamycin, are implicated frequently (1–6). Less frequently incriminated are erythromycin, aminoglycosides, fluoroquinolones, sulfamethoxazole-trimethoprim, and perhaps surprisingly, both vancomycin and metronidazole, which are the drugs of choice for treatment of *C. difficile* diarrhea. Tetracyclines and chloramphenicol are now rarely implicated, but they were frequently implicated in what was diagnosed as staphylococcal enterocolitis in the early antibiotic era (1, 5, 13). *C. difficile* diarrhea occurs both sporadically and in clusters or outbreaks in hospitals, nursing homes and chronic care facilities, but the frequency of the disease is very much lower in the community. *C. difficile* can be detected in the stools of 5% or more of healthy adults, and even more frequently in the stools of healthy infants (30–50%) and patients without diarrhea in some hospitals and nursing homes (up to 30%). Infants who carry the organism rarely develop *C. difficile* colitis, and there is evidence suggesting the reason for this apparent protection is that the toxins do not bind well to the colonic mucosa because its binding sites are immature (3, 5, 6). *C. difficile* is widely distributed in the soil, water, and environment of patients with *C. difficile* diarrhea (14). In some hospitals and nursing homes, as many as 20–30% or more of patients who have received antibiotics have been found to be asymptomatic carriers and shedders of the organism into the environment. Consequently, spread of the

organism to others there who have been treated with antibiotics and are therefore susceptible to colonization by small numbers of *C. difficile* spores may be frequent. Transmission of the *C. difficile* seems most often to be via the hands of hospital personnel, and also by contact with contaminated surfaces and fomites (11, 13).

CLINICAL MANIFESTATIONS OF *C. DIFFICILE* DIARRHEA

The typical manifestations of *Clostridium difficile* diarrhea are cramping abdominal pain, profuse diarrhea consisting of mucoid, greenish, foul-smelling, watery stools, low grade fever, and leukocytosis. These can start a few days after antibiotic therapy is begun or *up to 8 weeks after its discontinuation*. Many patients with *C. difficile* diarrhea have fever that exceeds 40°C and leukocytosis as high as 50,000 per mm³ (3); in fact, leukemoid reactions in the range of 100,000 per mm³ have been reported. It is not rare for patients to have watery diarrhea similar to that seen in the benign antibiotic diarrhea of unknown cause (1–6). Although colitis can occur throughout the colon, it is usually most severe in the distal colon and rectum. When patients develop colitis localized to the cecum and right side of the colon, they may have little or no diarrhea. Instead, fever, marked right-sided lower abdominal pain and tenderness, marked leukocytosis, and decreased intestinal motility may be the only clues to the disease. This presentation is not rare but is especially serious, in part because diagnosis and treatment may be delayed because of the lack of diarrhea, and seems to occur more frequently when antiperistaltic agents or opiates have been given postoperatively. Unless endoscopy or computerized tomography or other tests are done and suggest the diagnosis and the need for specific antibiotic therapy, these patients may progress rapidly in severity and require emergent abdominal laparotomy and subtotal colectomy because of toxic megacolon or colonic perforation (15, 16). Other complications of *C. difficile* diarrhea include dehydration, hypovolemia, hypoalbuminemia, anasarca, electrolyte disturbance, shock, and a reactive arthritis (4–6).

The differential diagnosis of *C. difficile* diarrhea includes benign or simple antibiotic-associated diarrhea, acute and chronic diarrhea caused by other enteric pathogens, adverse reactions to various medications other than antibiotics, ischemic colitis, idiopathic inflammatory bowel diseases, and intra-abdominal sepsis.

DIAGNOSIS OF *C. DIFFICILE* DIARRHEA AND COLITIS

Endoscopic diagnosis

Guidelines for diagnosis are presented in Table 1. The best and most rapid way to establish the diagnosis of *C. difficile* colitis is by endoscopy with biopsy of suspicious lesions, but endoscopy is expensive and usually reserved for

TABLE 1

Practice Guidelines for Diagnosis of Clostridium difficile Diarrheal Syndromes

1. The diagnosis should be suspected in anyone with diarrhea who has received antibiotics within the previous 2 months and/or whose diarrhea began 72 h or more after hospitalization.
2. When the diagnosis of *C. difficile* diarrhea is suspected, a single stool specimen should be sent to the laboratory for testing for the presence of *C. difficile* and/or its toxins.
3. If the results of those tests are negative but diarrhea persists, one or two additional stools can be sent for testing with the same or different tests.
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 is not available, or when other colonic diseases are in the differential.

special situations, such as when the patient is seriously ill and the results of rapid but not highly sensitive noninvasive tests are negative or delayed and *C. difficile* diarrhea is strongly suspected, or when some other disease process that can be diagnosed by endoscopy is also being considered (2–6). Endoscopy is diagnostic when it demonstrates characteristic, raised, yellowish nodules or plaque-like pseudomembranes, often with skip areas of normal mucosa. The nodules are usually 2–10 mm in diameter, but in advanced stages they are increased in number, enlarged, and coalesced to form plaques or membranes that cover large segments of the inflamed mucosa but are easily stripped from it (hence the term pseudomembrane). Nodules and small pseudomembranes are easily dislodged during the processing of biopsies. Microscopic examination of the lesions shows epithelial necrosis, goblet cells distended with mucus, edema, and infiltration of the lamina propria with leukocytes, epithelial cells, fibrin, and mucin. The terms “summit lesions” or “volcano lesions” have been used to describe these lesions (1, 3, 4). Gross lesions may be so characteristic to experienced endoscopists that biopsy is not needed, but it is best to obtain a biopsy if there is doubt about the diagnosis. When the colonic mucosa shows only erythema, friability, or edema without nodules or pseudomembranes, it is suggestive of the so-called nonspecific colitis or simple colitis that may be caused by *C. difficile* as well as a variety of other conditions. Biopsy of such lesions, even when small, may confirm the presence of inflammation (colitis) along with pseudomembranes that are not grossly apparent. In a study of 22 patients with pseudomembranous colitis, it was found that endoscopy with a rigid endoscope detected fewer cases of colitis than with a flexible sigmoidoscope (77 vs 91%), and that colonoscopy detected additional cases (9% of the total) not reached using flexible sigmoidoscopy (17).

C. difficile-specific diagnostic tests

There is as yet no simple, inexpensive, rapid, sensitive, and specific test for diagnosing *C. difficile* diarrhea and colitis, nor are all the available tests suitable for adoption by

every laboratory (18). However, each laboratory should consider providing one of the rapid, inexpensive tests and also, if practical, a specific test for the presence of the organism or its toxins. Many institutions provide an enzyme immunoassay (EIA) test for rapid detection of toxin A or B and also a cell culture assay for toxin B, the cytotoxin.

Tissue culture tests for toxin B. The “Gold Standard” laboratory test for establishing the diagnosis of *C. difficile* colitis is still the demonstration in cell culture monolayers of the characteristic cytopathic effect of toxin B in filtrates of diarrheal stools. Specificity of the cytotoxicity is demonstrated by showing that it is prevented (neutralized) by use of antitoxin to *C. difficile* or *Clostridium sordellii* toxin (the utility of the latter reflects antigenic cross-reactivity) (1–6, 18–21). There is no practical laboratory test available for detecting toxin A in stools by means of its biological properties. Cell culture tests to detect the specific cytopathic effects of toxin B are positive in more than 90% of patients with pseudomembranous colitis (1–6). False negative results in this as well as the other tests used for detecting these toxins may be caused by a number of factors: because of the inactivation of the heat and acid labile toxins during storage or transportation or by medications, because some cell lines used for this test are less sensitive than others to the cytopathic effect of the toxin (2–6), and especially because of testing stool specimens diluted in the laboratory. Therefore, it is important to recognize that a negative test for toxin B in cell cultures does not rule out *C. difficile* as the cause of the diarrhea. If toxin B is detected in high titer, it is highly likely that *C. difficile* is the cause of the diarrhea, but there is little correlation in individual patients between the height of the toxin titer and the severity of the diarrheal disease. It is not uncommon for patients who have responded to appropriate therapy for *C. difficile* diarrhea to continue to have stools that test positive for toxin B or the organism for a short time after discontinuation of otherwise successful therapy. Experience has shown that most of these patients will have no further diarrhea and that it is not necessary to perform cultures or tests for the toxin on stools from patients who no longer have diarrhea (5, 6, 18, 22).

Enzyme immunoassay tests for toxin A and/or B. There are several commercially available EIA tests for detection of toxins A and/or B of *C. difficile* in stools (1–3, 5, 18–21). They are rapidly performed and relatively inexpensive when done in batches, and they are probably the most widely used laboratory aids in the United States in diagnosing *C. difficile* diarrhea. The EIA tests are more specific than they are sensitive. The sensitivity of the commercial EIA kits used for toxin A and B detection has varied widely when evaluated in different laboratories using the same kits but differing criteria for a positive endpoint. Whereas sensitivities have ranged from a low of about 70% to as high as 95%, specificity was generally very good. In most published reports, accuracy of these tests was evaluated on the basis of probable clinical diagnoses instead of upon diagnoses reached using both a cytotoxicity test for toxin B and en-

doscopy, arguably the two most accurate and dependable diagnostic aids. On average, EIA tests for toxin A and/or B failed to detect about 10% (range 5 to 33%) or more of cases of *C. difficile* diarrhea diagnosed clinically and by endoscopy with biopsy or by use of toxin B assays in cell cultures. Newer and allegedly better EIA tests (as well as other novel tests) are becoming available, but proper clinical studies documenting their superiority have not yet been reported. Therefore, it should be emphasized that a negative EIA test for toxins A or B does not rule out the diagnosis of *C. difficile* colitis. Sensitivity is rarely improved by sending more than one stool on the same day for EIA testing, so this practice is probably not cost-effective and should be discouraged. However, when an EIA test, or other rapid test, is reported negative, it may be then be worthwhile to send another stool the next day for testing by EIA or by different tests, especially if the patient with antibiotic diarrhea of unknown cause is critically ill or does not improve after antibiotic therapy has been discontinued and supportive therapy has been given. Alternatively, empiric therapy with metronidazole may be given to seriously ill patients when the first test result is negative and other diagnostic tests are not available or are in process.

Latex agglutination test. Originally thought to detect toxin A, this simple, rapid, and inexpensive immunologic test actually detects the presence of glutamate dehydrogenase produced by *C. difficile*, not toxin A (3, 4). This enzyme appears to play no role in the pathogenesis of *C. difficile* diarrhea, but many clinicians and laboratory personnel still incorrectly believe the latex agglutination test detects toxin A. Nontoxicogenic strains of *C. difficile* (which do not cause diarrhea) are also positive with the latex test. In addition, the latex agglutination test is nonspecific, because several other organisms commonly found in stools can produce an antigen that cross-reacts with the antibody directed against glutamate dehydrogenase produced by *C. difficile*. Overall, the latex agglutination test is about as sensitive as but not as specific as the EIA tests for the toxins (19–21, 23). Comments in the previous section discouraging the practice of sending more than one diarrheal stool per day for EIA testing apply equally well to the latex agglutination test.

Both the EIA and latex agglutination tests are simple, rapid, and inexpensive if they are performed in batches and quantity, but neither one is as reliable and sensitive as desired. Unfortunately, clinicians are often unaware of the specific test used for detecting *C. difficile* or its toxins in their laboratory and of their important differences in sensitivity and interpretation, in part because such results are commonly reported simply as a positive or negative “*C. difficile* test” without specifying the test used. A few laboratories have begun to use both the EIA and the latex agglutination tests, reserving the performance of the latter for specimens that are negative by the EIA. This strategy appears to improve sensitivity and to decrease specificity, but many clinicians would conclude this errs in the right

direction for a seriously ill patient. Others have used one of them along with a different test, such as a culture for the organism, or a cell culture monolayer test for the CPE of toxin B so as to maximize both the sensitivity, specificity, and rapidity of the reports they generate. If only one of the commonly available rapid tests can be performed, the enzyme immunoassays (EIA) for detecting toxins A or B are probably superior to the latex agglutination test. Finally, the practice of sending stools from patients without diarrhea to be tested for *C. difficile* or its toxins as a preoperative routine, and of giving the patient prophylactic metronidazole if the results are positive is to be discouraged on the grounds that it might hasten the spread of metronidazole-resistant strains of organisms such as *C. difficile* and *Helicobacter pylori*.

Stool cultures for detecting carriage of *C. difficile*. Since many healthy infants, children, and adults may be carriers of *C. difficile*, stool cultures may yield misleading or "false-positive" results in patients with simple antibiotic diarrhea because of coincidental intestinal carriage of the organism. In one study, about 25% of *C. difficile* isolates obtained from infants, healthy persons, and hospitalized patients with or without diarrhea were nontoxigenic (19) and presumably incapable of causing diarrhea. Conversely, in another study only about 10% of isolates from patients with antibiotic-associated diarrhea were nontoxigenic (20). Thus, whereas it is true that the isolation of *C. difficile* does not prove that it is the cause of a patient's antibiotic diarrhea, it is also the case that it is the most likely cause, especially if the isolate is toxigenic. Therefore, if a patient treated with antibiotics has severe diarrhea, a positive culture by itself might justify therapy with metronidazole, which is inexpensive and relatively safe. Other problems with stool cultures include that there is a delay of 2–3 days while awaiting results, that they are relatively expensive, and that not all laboratories have the facilities and expertise needed for isolation and identification of the isolate and for testing its toxigenicity. However, simple methods have become available for isolating the organism, particularly those using selective media containing cycloserine, cefoxitin, and fructose in agar and incubation in anaerobic jars or Gas-Paks, and for presumptively identifying the organism biochemically or by demonstrating its characteristic chartreuse color under UV light (2–4, 6, 24, 25). Few, if any, laboratories routinely perform antibiotic susceptibility tests on *C. difficile* isolates, but this test may become more necessary in the future because of the growing preference for using metronidazole for treatment and because occasional isolates are already resistant to metronidazole (about 3%).

Stool cultures for conventional enteropathogens. Experience has shown that antibiotic-associated diarrhea beginning 3 or more days after admission to the hospital is rarely caused by conventional enteric pathogens such as salmonella, shigella, campylobacter, or protozoa, and it is not cost-effective to obtain cultures or other studies for them unless tests for *C. difficile* are negative (26). However,

patients whose stools were negative for *C. difficile* and its toxins have occasionally developed pseudomembranous or nonspecific enterocolitis that was believed to be caused by staphylococci, salmonella, *Clostridium perfringens* type C, or other organisms (4, 13, 25). When a diagnosis of antibiotic-associated colitis is made in a patient with negative tests for *C. difficile* and/or its toxins, these organisms should be considered as the possible cause. In this situation, in addition to obtaining stool cultures for enteric pathogens, a stool culture for *Staphylococcus aureus* using selective media such as phenylethyl agar or mannitol salt agar should be requested along with a Gram's stained smear to look for leukocytes and large numbers of Gram-positive cocci in clusters. If these are positive, vancomycin should be used for treatment of enterocolitis because staphylococci are resistant to metronidazole (13, 25).

Other diagnostic aids

Screening tests. Abnormal numbers of fecal leukocytes are present in stained smears of diarrheal stools in about one-third of patients with *C. difficile* diarrhea (18, 24, 27). Even though the fecal leukocyte test is neither specific nor sensitive, it is simple and it can be useful *if done properly*. A positive test consists of detecting five or more leukocytes in three or more high-dry fields. Fecal leukocytosis is a nonspecific finding that may result from many causes, but when it is found in a patient who has been treated recently with antibiotics, the so-called simple or benign type of antibiotic diarrhea is quickly and effectively ruled out and *C. difficile* diarrhea becomes very likely. Methylene blue, Gram's, or Giemsa stains are most commonly used, but a Gram's stain is preferred, because detection of large numbers of Gram-positive cocci in clusters along with fecal leukocytes suggests the possibility of *S. aureus* enterocolitis, and also that stool cultures using media selective for staphylococci should be obtained (13).

Similarly, stools can be tested rapidly for the presence of lactoferrin, a product of leukocytes (28, 29). The presence of leukocytes or lactoferrin in stools from a patient with antibiotic-associated diarrhea is sufficient to justify beginning empiric therapy for *C. difficile* diarrhea in a severely ill patient.

Diagnostic imaging techniques and procedures. Abdominal radiologic studies, such as flat plates or scout films, may show an edematous or distended colon. They are of little value in diagnosis of early or mild cases of *C. difficile* diarrhea, but they can be helpful when complications such as toxic dilation or perforation of the colon develop. Barium contrast enemas are not very useful except in ruling out other conditions during early *C. difficile* diarrhea, and they may be dangerous at later stages. Computerized tomography (CT) may be useful in detecting evidence of colonic inflammation, edema, or pseudomembranes, findings that would be particularly important in patients with right-sided colitis who present with an acute abdominal syndrome without

TABLE 2

Practice Guidelines for Treatment of Clostridium difficile Diarrhea or Colitis

-
1. Antibiotics should be discontinued if possible.
 2. Nonspecific supportive therapy should be given, and is often all that is needed in treatment. Specific antibiotics should not be given routinely.
 3. When the diagnosis of *C. difficile* diarrhea is confirmed and specific therapy is indicated, metronidazole given orally is preferred.
 4. If the diagnosis of *C. difficile* diarrhea is highly likely and the patient is seriously ill, metronidazole may be given empirically before the diagnosis is definitely established.
 5. Vancomycin given orally is reserved for therapy of *C. difficile*-associated diarrhea until one or more of the following conditions are present:
 - (a) The patient has failed to respond to metronidazole.
 - (b) The patient's organism is resistant to metronidazole.
 - (c) The patient is unable to tolerate metronidazole, or is allergic to it, or is being treated with ethanol containing solutions.
 - (d) The patient is either pregnant or a child under the age of 10 years of age.
 - (e) The patient is critically ill because of *C. difficile*-associated diarrhea or colitis.
 - (f) There is evidence suggesting the diarrhea is caused by *Staphylococcus aureus*.
-

diarrhea, or in the early detection of complications of *C. difficile* diarrhea. However, because it is expensive, CT is reserved for special situations (30, 31). Radionuclide scans may detect evidence of colonic inflammation rapidly, but the findings are nonspecific, expensive, time-consuming, and not always readily available.

TREATMENT OF ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS

Nonspecific supportive therapy

Guidelines for treatment are presented in Table 2. When appropriate diagnostic measures are in progress, but the diagnosis of *C. difficile* diarrhea has not yet been established and the patient is not seriously ill, nonspecific supportive therapy should be given and is often all that is needed for resolution of diarrhea, even when it is caused by *C. difficile*. Nonspecific therapy may have the additional benefit of reducing the likelihood of a relapse, as compared to specific antibiotic therapy. Supportive therapy usually consists of replacement therapy with fluids and electrolytes. If possible, antibiotics given to treat an infection should either be discontinued or switched to alternate appropriate antibiotics. The administration of antiperistaltic and opiate drugs should be avoided, because they may mask the patient's symptoms and also cause pooling of toxin-laden fluids within the colon (2, 4). Some patients with *C. difficile* diarrhea have worsened after being given antiperistaltics or opiates, but this may have been coincidental (32), since many patients with the disease have been given antiperistaltics without any adverse consequences.

Specific antimicrobial therapy

When appropriate diagnostic tests have been performed and the diagnosis of *C. difficile* diarrhea is likely or confirmed, or the patient is a nonpregnant adult or a child over 10 yr of age who is worsening or has not responded to supportive therapy given for 2 or 3 days, specific antimicrobial therapy may be initiated. Metronidazole, vancomycin, teicoplanin (which is not available in the United States), and, less often, bacitracin have been used to treat *C. difficile* diarrhea because these antimicrobials inhibit growth and toxin production by *C. difficile*. Metronidazole and vancomycin are by far used most often in the United States. Therapy given by the oral route is *always* preferred, because *C. difficile* diarrhea is not caused by tissue invasion, and the toxins produced by the organism within the intestinal lumen cause diarrhea only after binding to specific receptors on the colonic mucosa. *C. difficile* diarrheal syndromes usually respond well to oral therapy with either metronidazole or vancomycin if therapy is started early enough, but the response is sometimes less good when metronidazole or vancomycin are given to patients who are critically ill with the disease (1–6).

A controlled study comparing therapy of *C. difficile* diarrhea with either metronidazole given orally in a dose of 250 mg four times per day or vancomycin in a dose of 500 mg four times per day for 10 days showed that the only statistically significant difference between them was that vancomycin was more costly (33). The duration of diarrhea and the frequency of side effects, posttreatment relapses, and carriage of the organism in convalescence were not significantly different. All 52 patients given vancomycin were cured, but 2 of 42 patients failed to respond to metronidazole (a difference that was not statistically significant), and were cured when therapy was changed to vancomycin, a fact that has led some investigators to prefer vancomycin when the patient is critically ill. Interestingly, 34 (22.8%) of the 149 patients in this study responded to supportive therapy alone within a 48- to 72-h observation period while the diagnosis was being established, and did not require therapy with either vancomycin or metronidazole. Specific oral therapy with metronidazole or vancomycin is usually given for only 7 to 10 days, unless the illness is severe or the diarrhea is slow to resolve (1, 2, 4, 33). Patients who require therapy for more than 10 days often have severe colitis, or a delay in diagnosis and treatment of colitis, or an underlying condition predisposing to diarrhea, such as lactose intolerance, irritable bowel disease, diabetic enteropathy, or diarrhea due to an adverse reaction to medications or diet.

Metronidazole given *intravenously* has been used to treat pseudomembranous colitis in patients who are unable to take it orally. The reported results have been good, although treatment failures have occurred. A possible explanation for treatment failures when metronidazole is given intravenously is that the stool concentrations achieved are usually

lower than those required for inhibition of the organism *in vitro* (34). Even though stool concentrations are also low when metronidazole is given orally (34, 35), such therapy is usually successful, and this paradox is as yet unexplained. Nonetheless, the oral route is preferred when it can be used because a wealth of clinical experience indicates it is highly efficacious.

Oral metronidazole (Flagyl) is preferred for therapy of C. difficile diarrhea. An expert committee of hospital infection control practitioners has recently recommended that metronidazole is preferred for specific or empiric antimicrobial treatment of *C. difficile* diarrhea, and their recommendation has been widely adopted in the United States (36). One of the main reasons for their recommendation was their desire to curtail the use of vancomycin because of fear that its use will encourage the spread of vancomycin-resistant enterococci (VRE), and ultimately the emergence and spread of vancomycin-resistant staphylococci, whereas metronidazole will not. Other reasons included were that metronidazole is much less expensive than vancomycin, that it is well-tolerated when given orally for short periods, and that it is as effective as vancomycin for most patients (33). Although metronidazole has not been approved by the Food and Drug Administration specifically for treatment of *C. difficile* diarrhea, it has been approved by the FDA for the treatment of serious infections caused by susceptible anaerobic bacteria such as *C. difficile*.

A few caveats concerning the preference for metronidazole are in order, because use of vancomycin for treatment of *C. difficile* diarrhea is justified in special circumstances. Although metronidazole is usually well-tolerated, it has an unpleasant metallic taste and may also cause nausea, vomiting, diarrhea, abdominal pain, pruritus, erythematous rashes, headache, confusion, dizziness, and reversible neutropenia, and additional patients may become allergic to it. Patients taking oral metronidazole should be cautioned against drinking alcoholic beverages because this might result in disulfiram (Antabuse)-like reactions. Also, rare isolates of *C. difficile* are resistant to metronidazole *in vitro*, although there is little evidence that resistance is responsible for treatment failures. At the University of Michigan Hospitals, 6 (3%) of 200 isolates of *C. difficile* obtained from patients and tested *in vitro* over the period from 1980 to 1990 were resistant to metronidazole at concentrations ranging from 16 to 128 µg/ml, whereas all were highly susceptible to vancomycin (37). Because metronidazole is a carcinogen, mutagenic in some animal species and *in vitro*, crosses the placental barrier and is fetotoxic for pregnant mice, it should be used during pregnancy only if clearly needed. Similarly, because the safety of metronidazole for children has not been proven, many prefer not to use it for treatment of children unless necessary.

For treatment of adults with *C. difficile* diarrhea, metronidazole is usually given orally in a dosage of 250–500 mg four times per day or 500–750 mg three times per day for 7–10 days; for children, a dosage of 35–50 mg/kg/24 h

TABLE 3
Practice Guidelines for Management of Relapses

1. Reconfirm the diagnosis.
2. Discontinue medications that may be contributing to the diarrhea, and treat the patient with nonspecific supportive therapy.
3. If specific therapy is needed, treat the patient with a standard course of metronidazole given orally for 7 to 10 days, or with vancomycin, as in the Treatment Guidelines (Table 2).
4. When possible, avoid treating (minor) infections with antibiotics for the next 2 months after treatment of a relapse.
5. No treatment available in the United States has been proven to prevent recurrences. If the patient has suffered from multiple recurrences, consider using one of the following antimicrobial regimens with or without one of the other therapeutic measures as an adjunct. These are not presented in an order of preference.
 - (a) Oral metronidazole (or vancomycin, as in Table 3).
 - (b) Specific therapy with vancomycin or metronidazole given orally for 1 to 2 months, either intermittently (such as every other day or week) or with gradual tapering, with or without adjunctive therapy with an oral anion-binding regimen such as cholestyramine or colestipol begun near the end of antimicrobial therapy and gradually tapered.
 - (c) Oral vancomycin plus rifampin.
 - (d) Oral yogurt, *Lactobacillus* preparations, or *Lactobacillus GG*.
 - (e) *Saccharomyces boulardii* (500 mg orally twice daily), if available, may be given for 1 month, if the patient is not immunocompromised, beginning 4 days before a 10-day course of specific antibiotic therapy has been completed.
 - (f) Human immune globulin by intravenous infusion, for patients with documented deficiencies.

divided into three doses has been used. If metronidazole is used *intravenously* for treating patients who are critically ill and/or unable to tolerate oral medications, it can be used in a dosage of 500–750 mg three or four times per day. As stated earlier, metronidazole given intravenously for treatment of *C. difficile* diarrhea is probably not as reliable as either metronidazole or vancomycin given orally. Metronidazole should be used via the intravenous route for treatment of *C. difficile* diarrhea only when it is not possible to treat via the oral route, and never for reasons of convenience. When metronidazole is used intravenously to treat *C. difficile* diarrhea, consideration should also be given to the simultaneous use of vancomycin enterally, as discussed below.

Indications for treatment with vancomycin. Vancomycin still has a role in the management of *C. difficile* diarrhea, although it is a much smaller one than was the case before the recommendation that metronidazole is preferred for therapy of *C. difficile* diarrhea. Because vancomycin is poorly absorbed systemically when given orally, effective concentrations are easily achieved in stools and serious systemic side effects are rare (2–6). Nevertheless, vancomycin should not be used for treatment of *C. difficile* diarrhea unless the patient is unable to tolerate metronidazole, or because of the other indications outlined the Practice Guidelines in Table 3.

It should be pointed out here that pseudomembranous enterocolitis was a well-recognized clinical complication of

surgery in the preantibiotic and early antibiotic era, that it was commonly attributed to toxin-producing, antibiotic-resistant *S. aureus*, and that it was treatable with oral vancomycin. Some investigators have retrospectively questioned the role of staphylococci in the cause of those illnesses (1), and suggested they were actually caused by *C. difficile*, whose importance in this syndrome was not established until about 1978 (1, 13). Staphylococcal enterocolitis became very much less frequent in the 1960s after the introduction and use of vancomycin and semi-synthetic penicillinase-resistant β -lactam antimicrobials for treating staphylococcal infections. However, there is a considerable body of evidence suggesting that staphylococci can indeed cause diarrhea and colitis after the use of antimicrobials. Before the antibiotic era, many patients diagnosed with staphylococcal enterocolitis had extensive inflammatory lesions in the colon at postmortem examination, and often in the ileum, jejunum, and stomach as well (13). These findings are not characteristic of *C. difficile* diarrhea, although ileitis has occasionally been documented in patients with it, especially if they have an ileostomy (38). After recognition in the late 1970s of the important and unquestionably dominant role of *C. difficile* in the causation of antibiotic-associated pseudomembranous colitis, little attention was given to *S. aureus* as an etiologic agent of antibiotic-associated diarrhea or colitis. However, there is no question that diarrhea can be caused by *S. aureus*. For example, diarrhea is common in patients with the toxic shock syndrome caused by infection with enterotoxigenic staphylococci, often the site is one that is minor and hard to detect (39). More alarming is that methicillin-resistant *S. aureus* enteritis has been reported within the past few years as an important cause of antibiotic-associated enteritis in Japan in patients with negative studies for *C. difficile* and its toxins (13, 40). If these reports are confirmed outside of Japan, then enteritis caused by methicillin-resistant *S. aureus* and methicillin-sensitive *S. aureus*, organisms that are resistant to metronidazole, may emerge as an important complication of antibiotic use elsewhere, including in the United States. Such cases would most likely be recognized when patients with antibiotic-associated diarrhea presumed to be caused *C. difficile* failed to respond to treatment with metronidazole. Staphylococci may already cause more nosocomial diarrhea or colitis in the United States and other countries than is appreciated, in part because selective culture media and other tests needed to implicate this organism are neither widely available nor often used for patients with nosocomial antibiotic diarrhea. Finally, in 1978, three patients in hospitals in the United States were reported to have pseudomembranous colitis, which was well documented in two of them, and good laboratory studies failed to detect *C. difficile* and its toxins in their stools, but were positive for *S. aureus* and a unique cytotoxin similar to one produced by their staphylococci *in vitro* (41). Therefore, it is possible that the preference for metronidazole in treatment of *C. difficile* diarrhea may be associated in the future with a resurgence of

diarrhea and enterocolitis caused by staphylococci. These issues are discussed in greater detail elsewhere (13).

When therapy with vancomycin for *C. difficile* diarrhea is justified, it is usually given orally in a dosage of either 125 mg four times per day for 7–10 days, or 500 mg four times per day if the patient is critically ill or has impending ileus, colonic dilation, or perforation. These regimens seemed equally effective in reported studies (4, 22). For infants and children, an oral dose of 500 mg/1.73 m² every 6 h has been used. Vancomycin should not be given intravenously as the sole therapy for *C. difficile* diarrhea, since effective concentrations within the colonic lumen are not reliably achieved when it is given in this way. If patients cannot be treated orally with vancomycin, or they have paralytic ileus, and the patient is to be treated by the instillation of the drug by perfusion via a tube or pigtail catheter directly into the cecum or ileostomy, 200 or 500 mg vancomycin in 500 ml (400 or 1000 μ g/ml) given up to four times per day can be used, if tolerated. Another regimen that has been used in this setting consists of giving vancomycin intracolonic (2000 mg followed by 100 mg every 4 h and 100 mg after each stool) via a pigtail catheter positioned during colonoscopy (42). Reconstituted solutions containing vancomycin must be diluted with at least 100 ml of diluent per 500 mg vancomycin.

Alternative therapies. Bacitracin (43), teicoplanin (44), or nonabsorbable anion binding resins (45) such as cholestyramine or colestipol may be given orally for treatment of mild *C. difficile* diarrhea (4), but these agents are neither as reliable nor as rapidly effective as metronidazole or vancomycin. Anion binding resins bind toxin B of *C. difficile*, but experience suggests their capacity to do this is limited and probably inadequate in severe cases. They may also bind vancomycin and thereby diminish its efficacy, and can cause severe constipation and intestinal obstruction once diarrhea has resolved. Neither teicoplanin nor bacitracin for oral administration are readily available in the United States. It should be cautioned that teicoplanin has a propensity similar to that of vancomycin for encouraging the spread of vancomycin-resistant enterococci, and that the clinical response to bacitracin is slower and less certain than it is with vancomycin, possibly because some isolates are resistant to bacitracin (37).

MANAGEMENT OF RELAPSES OR RECURRENCES OF *C. DIFFICILE* DIARRHEA OR COLITIS

Guidelines for management of relapses are presented in Table 3. Relapses (recurrences) of diarrhea or colitis are recognized when there is a return of symptoms, signs and positive diagnostic tests a few weeks to months after discontinuation of *successful* antibiotic therapy for *C. difficile* diarrhea. Because the patients had previously responded, these occurrences should not be thought of as treatment failures. Relapses occur in about 15–35% of patients, with a mean frequency of about 20% (4, 22, 23). Because *C.*

difficile diarrhea and colitis have markedly increased in frequency in hospitals in the United States since 1984 (11, 46), so has the frequency of encountering patients with recurrent or relapsing *C. difficile* diarrhea. Relapsing *C. difficile* diarrhea is a serious, difficult, and still unsolved management problem, especially when patients have experienced three or more episodes (47). However, it is important to remember is that it is rarely difficult to treat each recurrence successfully using standard therapy with metronidazole (or vancomycin); what is still difficult to accomplish is the prevention of further recurrences.

Recurrences may be caused either by persistence of the original strain of *C. difficile* or by reinfection with the same or a different strain. Some strains seem more likely than others to cause recurrences (47), whereas strains that are nontoxicogenic never do so. Recurrences usually begin with the return of diarrhea 2 wk to 2 months after successful antimicrobial therapy of an episode of *C. difficile* diarrhea. Recurrences are characterized by the return of typical symptoms and signs of *C. difficile* diarrhea, positive assays for *C. difficile* toxins in stools, and cultures that yield vancomycin and metronidazole susceptible strains of *C. difficile*. The frequency of recurrences does not seem to be influenced by the specific nature of the original inciting antibiotic, by whether metronidazole or vancomycin was used for treatment of the initial episode, or by the dosage or duration of treatment with vancomycin or metronidazole. In some reports, recurrences occurred more often in patients whose stool cultures remain positive after successful antibiotic therapy for *C. difficile* diarrhea, but not in others (29, 47). In either case, because there is no way to reliably eradicate the *C. difficile* carrier state, there is no good reason to obtain stool cultures to determine whether a patient is at high risk for a relapse. Relapses appear to be less likely to occur if the first episode was treated only with supportive therapy. Some unfortunate patients have experienced many recurrences; more than 6 episodes is not unusual and more than 20 is alleged to be the record, each after a course of apparently successful treatment. Fortunately, patients can be reassured that recurrences do *not* have a tendency to become progressively more severe (47), even though they may cause more and more concern with each episode.

Many different treatments have been used in an attempt to prevent recurrences, and most experts have their own favorite regimen. However, *no specific treatment regimen commercially available in the United States has been proven in properly controlled, double blinded, randomized studies to prevent multiple recurrences or relapses of C. difficile diarrhea*. Standard antibiotic therapy should be used to treat relapses and is usually successful, even if it does not prevent further recurrences (47). Metronidazole seems to be as effective as vancomycin in treatment of relapses, and it is less expensive and generally well tolerated. There is little or no evidence that patients suffering from multiple recurrences do so because they have underlying abnormalities of their gastrointestinal tract or host

resistance factors that accounts for their proclivity for development of recurrences, although a few children and one adult have been reported who may have had a specific immunoglobulin deficiency that predisposed them to relapses (48–50). Whereas vancomycin and metronidazole almost always kill the vegetative forms of *C. difficile* that produce the toxins causing diarrhea, they do not reliably kill the spore forms of the organism, the persistence of which seems the root cause of the trouble. In fact, antimicrobial treatment appears to encourage formation of spores (51), which are hardy and can persist in the intestines or environment of patients for long periods of time (14), during which they may germinate, or the patient may become reinfected, and diarrhea may occur if the patient has not re-established intestinal resistance to the colonization, growth and toxin production by *C. difficile*. The mechanisms, such as competition for nutrients (52), by which certain organisms of the normal flora are responsible for “colonization resistance” to *C. difficile* are poorly understood. Paradoxically, derangements in colonization resistance are even seen after treatment with vancomycin and metronidazole, since both are capable of inducing *C. difficile* diarrhea as well as of treating it. Unfortunately, the fecal flora and its colonization resistance may not return to normal for many months after exposure of patients to antibiotics. It therefore seems prudent that an effort should be made in managing patients experiencing relapses to avoid the use of antibiotics as much as possible so as to hasten the return of the protective normal fecal flora. Accordingly, it is recommended that the *unnecessary* prophylaxis or treatment of infections, especially minor ones, with antibiotics should be avoided within the first 2 months after treatment of an episode of *C. difficile* diarrhea (47).

When patients experience a recurrence of *C. difficile* diarrhea within a few months after a successfully treated episode, the diagnosis should again be confirmed (especially if the episode is atypical). Unless diarrhea is mild, the patient should again be treated specifically, preferably with metronidazole, even if it was used for treatment of the first episode (or vancomycin, according to the treatment Guidelines in Table 3), usually for only 7–10 days in standard doses if the patient responds promptly (47).

Some authorities believe that patients suffering from repeated recurrences should be treated using a regimen consisting of the intermittent administration of metronidazole (or vancomycin) over a period of weeks or even months and followed by their gradual tapering, or by prophylaxis with low doses of these antibiotics given daily or on alternating days or weeks, or by use of cholestyramine or other anion binding medications along with specific antibiotics, especially at the end of therapy (6, 53). Cholestyramine can bind vancomycin as well as the toxins of *C. difficile* and as a result may interfere with specific therapy; it may also cause obstipation as a side effect. Such regimens may appear to have been successful in preventing further relapses, but none have been validated in properly controlled studies, so

the favorable result may be only coincidental. Treatment with the combination of vancomycin and rifampin given orally was thought to be effective in termination of relapses in a small uncontrolled study (54), but there is no evidence that this antimicrobial combination has any synergistic or other unique activity against *C. difficile* or its spores, the hope of which was the reason it was tried in the first place.

Various other unproven measures have tried to restore the colonization resistance of the fecal flora of patients with relapses. Many of them fall into a category referred to as probiotics. These include the oral or rectal administration of yogurt, lactobacilli (55), enemas containing feces from healthy persons (56) or mixtures of various bacteria normally found in the intestinal tract (57). Use of the *Lactobacillus GG* strain seems to be more effective and rational than yogurt or other lactobacilli (55). Another promising new approach involves treating patients who have relapsed with the oral administration of a live yeast (*Saccharomyces boulardii*) for about 4 wk, beginning 4 days before the end of conventional antibiotic therapy for a recurrence. This novel measure was evaluated in the United States in a well designed multicenter placebo-controlled study and was reported to be safe as well as effective. Its use in patients who had experienced at least one relapse was associated with a reduction of about 50% ($p = 0.04$) in the frequency of further relapses (58) compared with those receiving placebo. This report is the only well controlled and scientific study concerning the prevention of relapses in humans that has thus far been reported. The mechanism of the presumed protective effect of *S. boulardii* is not known, but it may be because a protease it produces prevents the binding of the toxins to the intestinal mucosa (59). Because *S. boulardii* is available for treating relapses in Europe but not in the United States, some physicians here have attempted to use *Saccharomyces cerevisiae* (Brewer's yeast) in a similar fashion. However, these two organisms are significantly different from one another (60), and there are no reports proving the efficacy of *S. cerevisiae*, although there are a few anecdotal reports claiming success with it.

Therapy with intravenous immune globulin, especially in children with various immunoglobulin deficiencies, has appeared effective in prevention of recurrences in anecdotal reports (48–50). Other novel ways to actively or passively immunize patients against *C. difficile* and its toxins are the subject of ongoing research related to this important and increasingly frequent problem of recurrent *C. difficile* diarrhea.

PREVENTION OF *C. DIFFICILE* DIARRHEA AND COLITIS

Guidelines for prevention are presented in Table 4. Prevention of *C. difficile* diarrhea and colitis is based upon a few simple practices and attitudes. Hospitalization and intensive exposure to antibiotics are important risk factors for acquisition of *C. difficile* (4–6, 8, 11, 12). Avoidance of the

TABLE 4

Practice Guidelines for Prevention of *Clostridium difficile* Diarrhea

1. Limit the use of antimicrobial drugs.
2. Wash hands between contact with all patients.
3. Use enteric (stool) isolation precautions for patients with *C. difficile* diarrhea.
4. Wear gloves when contacting patients with *C. difficile* diarrhea/colitis or their environment.
5. Disinfect objects contaminated with *C. difficile* with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide.
6. Educate the medical, nursing, and other appropriate staff members about the disease and its epidemiology.

unnecessary use of antimicrobial drugs is of obvious importance, but is all too often easier said than done. Restraints and limitations in the use of antimicrobials are of growing importance because of alarming recent increases in the emergence of new antibiotic-resistant pathogens in hospitals, such as *Enterococcus faecalis* and *E. faecium*, *Streptococcus pneumoniae*, *Staphylococcus hemolyticus*, *Clostridium difficile*, and numerous species of enteric Gram-negative bacilli.

Transmission of *C. difficile* from one person to another via the hands of personnel appears in hospitals to be more important in spread of *C. difficile* than does contact with spores in the environment, but both probably occur. Careful handwashing before and after contact with all patients, and the use of gloves and stool (enteric) isolation precautions when contacting patients with *C. difficile* diarrhea or who are carriers of this organism are the most effective measures for preventing its spread (4, 14, 61, 62). Single rooms with private bathrooms should be provided when possible for patients with *C. difficile* diarrhea, at least until their diarrhea has stopped. Patients with *C. difficile* diarrhea and to a lesser extent, those who are asymptomatic carriers of the organism appear to contaminate their immediate environment with *C. difficile* spores, which then becomes a potential source of reinfection for the patient as well as personnel and other persons, particularly if they have recently received antibiotics (8, 14). Since many healthy persons and patients without diarrhea who are in hospitals carry *C. difficile* in their intestines, there is little if any rationale for continuing Enteric Isolation Precautions for patients who no longer have diarrhea, or to test them for carriage of the organism after diarrhea has stopped. Antibiotics do not reliably kill the spores of *C. difficile* even though they may kill the vegetative forms of the organism, and therefore treatment of carriers with metronidazole or vancomycin does not eradicate the organism from their intestinal tracts (35), even though these antibiotics may markedly decrease the numbers of vegetative forms in stools (51). Suppression of excretion of the organism by carriers with use of treatment with metronidazole or vancomycin may have occasionally been useful in terminating localized outbreaks in hospitals, but the effects of this approach have been far from striking. Alkaline glutaraldehyde, sodium hypochlorite, and ethylene oxide are

effective in killing the spores as well as the vegetative forms of *C. difficile* (4, 11, 14) that persist on fomites, instruments and contaminated surfaces, but none of these are satisfactory for handwashing, which is still best carried out with ordinary disinfectant soaps or chlorhexidine, despite their limited power to kill *C. difficile* spores (4, 63). Additional measures that have been used in facilities where *C. difficile* diarrhea is occurring at a high rate include identifying and cohorting (segregating) patients who are carriers, restricting patients who are carriers to single rooms with private bathrooms, and antibiotic control programs. Neither vancomycin nor metronidazole nor any other antimicrobial regimen are reliably effective in eradicating the *C. difficile* carrier state, probably because the spores of the organism are resistant to their action, unlike the vegetative forms.

It is important that *everyone* involved with patient care in hospitals, nursing homes, and at home be educated about the organism and its epidemiology, about rational approaches to the treatment and care of patients with *C. difficile* diarrhea, about the importance of handwashing between contact with patients, about the use of gloves when caring for a patient with *C. difficile* diarrhea, and about the avoidance of the unnecessary use of antimicrobials.

ACKNOWLEDGMENTS

The author acknowledges with sincere thanks and gratitude the expert advice, help, and counsel of the Practice Parameters Committee of the American College Gastroenterology: J. Patrick Waring, M.D., F.A.C.G. Chair (Emory University, Atlanta, GA), Alan Barkun, M.D. (Montreal General Hospital, Montreal, PQ, Canada), W. Scott Brooks, M.D. (Atlanta, GA), Kenneth R. DeVault, M.D., F.A.C.G. (Mayo Clinic, Jacksonville, FL), John Hughes, M.D., F.A.C.G. (Kelsey Seybold Clinic, Houston, TX), Douglas M. Simon, M.D., F.A.C.G. (Albert Einstein Medical School, New Rochelle, NY), Thomas Viggiano, M.D., F.A.C.G. (Mayo Clinic, Rochester MN), James Achord, M.D., F.A.C.G. (University of Mississippi Medical Center, Jackson, MS), Eugene M. Bozymski, M.D., F.A.C.G. (University of North Carolina, Chapel Hill, NC), Stephen H. Caldwell, M.D. (University of Virginia HSC, Charlottesville, VA), Michael J. Goldberg, M.D. F.A.C.G. (Chicago, IL), Simon K. Lo, M.D., F.A.C.G. (Harbor–University of California Los Angeles Medical Center, Torrance, CA), Robert H Squires, Jr., M.D. (University of Texas Southwestern Medical Center, Dallas, TX), Paul Yeston, M.D. (University of Virginia Health Sciences Center, Charlottesville, VA), Peter A. Banks, M.D., F.A.C.G. (Brigham and Women's Hospital, Boston, MA), Patrick G. Brady, M.D., F.A.C.G. (J. A. Haley Veterans Administration Hospital, Tampa, FL), William D. Carey, M.D., F.A.C.G. (Cleveland Clinic Foundation, Cleveland, OH), Norman D. Grace, M.D., F.A.C.G. (Faulkner Hospital, Boston, MA), George W. Meyer, M.D., F.A.C.G. (Georgia Baptist Medical Center, Atlanta, GA), Namish Vakil, M.D., F.A.C.G. (Sinai Samaritan Medical

Center, Milwaukee, WI), Gregory Zuccaro, Jr., M.D. (Cleveland Clinic, Cleveland, OH).

Reprint requests and correspondence: Robert Fekety, M.D., Division of Infectious Diseases, Department of Internal Medicine, 3116 Taubman Health Center, University of Michigan Hospitals and Medical School, Ann Arbor, MI 48109-0378.

REFERENCES

- Bartlett JG. Treatment of *Clostridium difficile* colitis. *Gastroenterology* 1985;89:1192–5.
- Fekety R, Shah A. Diagnosis and treatment of *C. difficile* colitis. *JAMA* 1993;269:71–5.
- Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. *N Engl J Med* 1994;330:257–62.
- Fekety R. Antibiotic-associated colitis. In: Mandell G, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 4th ed. New York: Churchill Livingstone, 1996, pp 978–806.
- Mitty RD, LaMont T. *Clostridium difficile* diarrhea: Pathogenesis, epidemiology, and treatment. *Gastroenterologist* 1994;2:61–9.
- Bartlett JG. *Clostridium difficile*: History of its role as an enteric pathogen and the current state of knowledge about the organism. *Clin Infect Dis* 1994;18(suppl 4):S265–72.
- Cudmore M, Silva J, Fekety R, et al. *Clostridium difficile* colitis associated with cancer chemotherapy. *Arch Intern Med* 1982;142:333–5.
- Johnson S, Gerding D. *Clostridium difficile*. In: Mayhall CG, ed. *Hospital epidemiology and infection control*. Baltimore: Williams & Wilkins, 1996, pp 399–408.
- Riegler M, Sedivy R, Pothoulakis C, et al. *Clostridium difficile* toxin B is more potent than toxin A in damaging human colonic mucosa *in vitro*. *J Clin Invest* 1995;95:2004–11.
- Qualman S, Petric M, Karmali M, et al. *Clostridium difficile* invasion and toxin circulation in fatal pediatric pseudomembranous colitis. *Am J Clin Pathol* 1990;94:410–6.
- McFarland LV, Mulligan ME, Kwok RY, et al. Nosocomial acquisition of *Clostridium difficile*. *N Engl J Med* 1989;320:204–10.
- Wilcox M. Cleaning up *Clostridium difficile* infection. *Lancet* 1996;348:767–8.
- Fekety R. Staphylococcal enterocolitis and diarrhea. In: Crossley K, Archer G, eds. *Staphylococcal infections*. New York: Churchill Livingstone, 1997.
- Kim K-H, Fekety R, Batts DH, et al. Isolation of *Clostridium difficile* from the environment and contacts of patients with antibiotic-induced colitis. *J Infect Dis* 1981;143:42–50.
- Medich DS, Lee KK, Simmons RL, et al. Laparotomy for fulminant pseudomembranous colitis. *Arch Surg* 1992;127:847–52.
- Triadifopoulos G, Hallstone AE. Acute abdomen as presentation of pseudomembranous colitis. *Gastroenterology* 1991;100:685–91.
- Tedesco FJ. Antibiotic-associated pseudomembranous colitis with negative proctosigmoidoscopic examination. *Gastroenterology* 1979;77:295–7.
- Gerding DM, Brazier JS. Optimal methods for identifying *Clostridium difficile* infections. *Clin Infect Dis* 1993;16(suppl 4):S439–42.
- Martirosian G, Meisel-Mikolajczyk F, Stanczak J, et al. Toxicogenicity of *Clostridium difficile* strains isolated in the surgical ward. *Acta Microbiol Pol* 1995;44:47–53.
- Staneck JL, Weckbach LS, Allen SD, et al. Multicenter evaluation of four methods for *Clostridium difficile* detection: ImmunoCard *C. difficile*, cytotoxin assay, culture, and latex agglutination. *J Clin Microbiol* 1996;34:2718–21.
- Barbut F, Kajzer C, Planas N, et al. Comparison of three enzyme immunoassays, a cytotoxicity assay, and toxigenic culture for diagnosis of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol* 1993;31:963–7.
- Fekety R, Silva J, Kauffman C, et al. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: Comparison of two dosage regimens. *Am J Med* 1989;86:15–9.
- Lyerly DM, Barroso LA, Wilkins TD. Identification of the latex-test reactive protein of *C. difficile* as glutamate dehydrogenase. *J Clin Microbiol* 1988;29:2639–42.
- George WL, Sutter VL, Citron D, et al. Selective and differential

- medium for isolation of *Clostridium difficile*. J Clin Microbiol 1979; 9:214–9.
25. Fekety R. Antibiotic-associated diarrhea and colitis. Curr Opin Infect Dis 1995;8:391–7.
 26. Anglim A, Farr B. Nosocomial gastrointestinal infections. In: Mayhall CG, ed. Hospital epidemiology and infection control. Baltimore: Williams & Wilkins, 1966, pp 196–225.
 27. Marx CE, Morris A, Wilson ML, et al. Fecal leukocytes in stool specimens submitted for *Clostridium difficile* toxin assay. Diagn Microbiol Infect Dis 1993;16:313–5.
 28. Guerrant RL, Araiys V, Soares E, et al. Measurement of fecal lactoferrin as a marker of fecal leukocytes. J Clin Microbiol 1992;30:1238–42.
 29. Miller JR, Barrett LJ, Kotloff K, et al. A rapid test for infectious and inflammatory enteritis. Arch Intern Med 1994;154:2660–4.
 30. Boland GW, Lee MJ, Cats A, et al. Pseudomembranous colitis: Diagnostic sensitivity of the abdominal plain radiograph. Clin Radiol 1994; 49:473–475.
 31. Boland GW, Lee MJ, Cats AM, et al. Antibiotic-induced diarrhea: Specificity of abdominal CT for the diagnosis of *Clostridium difficile* disease. Radiology 1994;191:103–6.
 32. Novak E, Lee JE, Seckman CE, et al. Unfavorable effect of atropine-diphenoxylate (Lomotil) therapy in lincomycin-caused diarrhea. JAMA 1976;235:1451.
 33. Teasley DG, Gerding DN, Olson MN, et al. Prospective randomized trial of metronidazole versus vancomycin for the treatment of *C. difficile* associated diarrhea and colitis. Lancet 1983;2:1043–6.
 34. Bolton RP, Culshaw MA. Fecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. Gut 1986;183:1169–72.
 35. Johnson S, Homann SR, Betten KM, et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or oral metronidazole. Ann Intern Med 1992;117:297305.
 36. Hospital Infection Control Advisory Committee. Recommendations for preventing the spread of vancomycin-resistant enterococci. Am J Infect Control 1995;23:87–94.
 37. Fekety R. Unpublished data.
 38. Tsutaoka B, Hansen J, Johnson D, et al. Antibiotic-associated pseudomembranous enteritis due to *Clostridium difficile*. Clin Infect Dis 1994;18:982–4.
 39. Larkin S, Williams D, Osterholm M, et al. Toxic shock syndrome: Clinical, laboratory, and pathological findings in nine fatal cases. Ann Intern Med 1982;96:858–64.
 40. Larkin S, Williams D, Osterholm M, et al. Toxic shock syndrome: Clinical, laboratory, and pathologic findings in nine fatal cases. Ann Intern Med 96;1992:858–97.
 41. Takesue Y, Yokoyama T, Kodama T, et al. Toxin involvement in methicillin-resistant *Staphylococcus aureus* enteritis in gastroenterological surgery. Gastroenterol Jpn 1991;26:716–9.
 42. Batts D, Silva J, Fekety R. Staphylococcal enterocolitis. In: Current chemotherapy and infectious diseases. Proceedings of the 11th ICC and the 19th ICAAC, Washington, D.C. American Society of Microbiology 1980:994–5.
 43. Pasic M, Jost R, Carell T, et al. Intracolonic vancomycin for pseudomembranous colitis. N Engl J Med 1993;329:583 (letter).
 44. Dudley MN, McLaughlin JC, Carrington J, et al. Oral bacitracin vs vancomycin therapy for *Clostridium difficile*-induced diarrhea. A randomized double blind trial. Arch Intern Med 1986;146:1101–4.
 45. de Lalla F, Nicolini R, Rinaldi E, et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhea. Antimicrob Agents Chemother 1992;36:2192–6.
 46. Kreutzer EW, Milligan FD. Treatment of antibiotic-associated pseudomembranous colitis with cholestyramine resin. Johns Hopkins Med J 1978;143:67–72.
 47. Jobe B, Grasley A, Deveney K, et al. *Clostridium difficile* colitis: An increasing hospital-acquired illness. Am J Surg 1995;169:480–3.
 48. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent *Clostridium difficile* disease. Clin Infect Dis (in press).
 49. Leung DY, Kelly CP, Boguniewicz M, et al. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by *Clostridium difficile* toxin. J Pediatr 1991;118:633–7.
 50. Hassett J, Meyers S, McFarland L, et al. Recurrent *Clostridium difficile* infection in a patient with selective IgG1 deficiency treated with intravenous immune globulin and *Saccharomyces boulardii* Clin Infect Dis 1995;20(suppl 2):S266–8.
 51. Onderdonk AB, Cisnoeros RL, Bartlett JG. *Clostridium difficile* in gnotobiotic mice. Infect Immun 1980;28:277–82.
 52. Wilson K, Perini F. Role of competition for nutrients in suppression of *Clostridium difficile* by the colonic microflora. Infect Immun 1988; 56:2610–4.
 53. Tedesco FJ. Treatment of recurrent antibiotic-associated pseudomembranous colitis. Am J Gastroenterol 1982;77:220–1.
 54. Buggy BP, Fekety R, Silva J. Therapy of relapsing *Clostridium difficile*-associated diarrhea with the combination of vancomycin and rifampin. J Clin Gastroenterol 1987;9:155–9.
 55. Gorbach SL. Successful treatment of relapsing *Clostridium difficile* colitis with *Lactobacillus GG*. Lancet 1987;2:1519.
 56. Schwan A, Sjolins, Trottestam U, et al. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of normal feces. Scand J Infect Dis 1984;16:211–5.
 57. Tvede M, Rask-Madsen J. Bacteriotherapy for chronic relapsing *Clostridium difficile* diarrhoea in six patients. Lancet 1898;1:1156–60.
 58. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. JAMA 1994; 271:1913–8.
 59. Pothoulakis C, Kelly CP, Joshi MA, et al. *Saccharomyces boulardii* inhibits *Clostridium difficile* binding and enterotoxicity in rat ileum. Gastroenterology 1993;104:1108–15.
 60. McFarland LV. *Saccharomyces boulardii* is not *Saccharomyces cerevisiae*. Clin Infect Dis 1996;22:200–1.
 61. Warny M, Denie C, Delmee M, et al. Gamma globulin administration in relapsing *Clostridium difficile* induced pseudomembranous colitis with a defective antibody response to toxin A. Acta Clin Belg 1995; 50:36–9.
 62. Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. Am J Med 1990;88:137–40.
 63. Bettin K, Clabots C, Mathie P, et al. Effectiveness of liquid soap vs. chlorhexidine gluconate for the removal of *Clostridium difficile* from bare hands and gloved hands. Infect Control Hosp Epidemiol 1994; 15:697–702.