Medical Staff Conference

Update on Pseudomembranous Colitis

Discussant
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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Every advance in medicine has its costs, and one of those associated with potent, often life-saving antibiotics is pseudomembranous colitis. I am pleased that my colleague at the University of California, Davis, Joe Silva, will review at this conference the important features of this disease, including its diagnosis, treatment, and prevention.*

JOSEPH SILVA, Jr, MD†: In 1893 Finney of Baltimore described pseudomembranous colitis in a patient who had recently undergone a gastrointestinal surgical procedure. Before the advent of antibiotics, as many as four to six cases would occur each year in large hospitals, generally following surgical treatment of the upper gastrointestinal tract. The frequent use of broad-spectrum antibiotics in the late 1960s to mid-1970s caused pseudomembranous colitis to become a frequent clinical disorder. In the days before the cause and appropriate treatment of pseudomembranous colitis were known, the mortality in symptomatic patients was as high as 20% to 25%. A little more than ten years ago, several groups determined that the disease is caused by colonic infection with toxigenic *Clostridium difficile,* a fastidious gastrointestinal anaerobe.

Clostridium difficile as a Pathogen

For many years, *C difficile* was infrequently identified as a cause of infection and was most often isolated in a cluster of other bacteria cultured from intra-abdominal abscesses, osteomyelitis, or gangrenous tissue. Small's discovery in 1969 that lincomycin hydrochloride induced fatal colitis in hamsters[1] led to a useful model that ultimately identified *C difficile* as the cause of pseudomembranous colitis in humans.[2-4] This anaerobic organism is a gram-positive, 15- to 20-μm bacillus that produces subterminal spores. The ability of these spores to survive for many years in an aerobic environment on inanimate surfaces may contribute to the greater incidence of colonization and of pseudomembranous colitis in patients in hospital.[5] Some 3% to 6% of healthy humans carry *C difficile,* and this prevalence may double or triple in patients in hospital. Colonization in these patients is related to the frequent prolonged use of high doses of antibiotics, which may radically alter the anaerobic microbial flora within the gastrointestinal tract. The incidence of colonization by *C difficile* is further increased in patients in hospital by manipulation of the intestinal tract, such as during the use of nasogastric tubes or enemas. Although *C difficile* is one of the first anaerobes to colonize the intestinal tracts of newborns, it almost never causes any clinical disease in this population. One possible reason for this paradox may be gleaned from preliminary data suggesting that neonatal tissues lack appropriate intestinal receptor sites for the toxins of *C difficile.*

Clostridium difficile appears to produce at least four toxins, two of which have been well characterized.[6] Toxin A (also called enterotoxin or D-1) is thought to account for much of the morbidity in the hamster model and in humans. This enterotoxin leads to perturbations in brush border function and in water transport across the intestinal tract; it is lethal to rodents. Toxin B (also named cytotoxin, or D-2) is defined by its primary effects on in vitro cell cultures of mammalian fibroblasts. The cytotoxin alters adenosine diphosphate ribosylation, thereby altering polymerization of intracellular actin filaments. As a result, actinomorphic changes occur 4 to 24 hours after inoculation of toxin B onto a monolayer of fibroblastic cells such as those used in isolating viruses. It appears that most clinical specimens isolated from patients are toxigenic, whereas as many as 20% to 25% of environmental isolates are nontoxigenic. Toxin B (cytotoxin) and toxin A (enterotoxin) are conjointly produced by most organisms that have been studied.

Clostridium difficile also produces two other toxins that interrupt gastrointestinal peristalsis. Toxins A and B are destroyed in vitro if subjected to repetitive cooling and warming. This fragility accounts for some of the varying results obtained by commercial laboratories testing for cytotoxin—false-negative results. Hamsters can be passively immunized and partially protected with γ-globulin against antibiotic-induced *C difficile* colitis.[7] Current efforts to develop toxoids are still fairly nascent, although it has been shown in the hamster model that a toxoid to the enterotoxin can induce immunity, whereas a toxoid to the cytotoxin does not.[8]

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Clinical Spectrum of Pseudomembranous Colitis

The principal symptom of pseudomembranous colitis is diarrhea. A useful clue to the diagnosis of colitis is the production of five or more loose stools a day.[9] Stools of patients with *C difficile* colitis are generally watery and small in volume and frequently contain mucus. It behooves clinicians to inquire of all patients who have watery diarrhea whether they have been taking antibiotics during the previous six weeks. Diarrhea develops in 15% to 25% of patients with pseudomembranous colitis after they discontinue their antibiotic(s). Physicians should also educate patients to report any diarrhea that exceeds five loose stools a day while receiving antibiotics. The pattern of diarrhea may be intermittent, with normal defecation for one to two days interspersed with days of five to ten episodes of diarrhea. Mucus is commonly noted in the stool, but blood is not. Many of our patients with colitis have negative fecal tests for occult blood. An increased number of fecal leukocytes are reported by some investigators, but in my experience this occurs in only about a third of specimens.

The clinical spectrum of pseudomembranous colitis is changing as assays for discovering the fecal toxins of *C difficile* become more available and employed. *Clostridium difficile* also can induce a syndrome of colitis that is well localized to the cecal area, and patients with this syndrome may not have diarrhea. Some also have hectic fever of >40°C (104°F) or fever of unknown origin, with minimal or no diarrhea. Other patients may have toxic megacolon or acute peritonitis. Physicians should be aware that the symptoms of pseudomembranous colitis may resemble those of an acute abdomen, and an inquiry should be made about recent antibiotic use.[10] Taking an astute history may spare a patient a laparotomy and will lead to appropriate treatment with an oral antibiotic regimen designed to eradicate *C difficile* from the colon.

Another form of clostridial enterocolitis occurs in patients with neutropenia from cancer chemotherapy.[11] The disorder of hemorrhagic or necrotizing cecitis (or typhlitis) is seen primarily in young patients who have leukemia. These patients usually have hectic fever, minimal stooling, and signs of an acute abdomen. Roentgenographs of the abdomen frequently show an absence of air in the right lower quadrant. The morbidity of this form of cecitis is high because of transmural inflammation and the high concurrence of bacteremia. Hematologists and oncologists must be aware of this disease, as it can be induced not only by antibiotic use but also by cytotoxic chemotherapeutic programs alone.[12] The progression from the onset of symptoms to death is rapid, occurring over a span of two to three days.

Pathogenesis and Incidence of Pseudomembranous Colitis

It is important to differentiate diarrhea with colitis from simple antibiotic-associated diarrhea. The latter state is more of a nuisance phenomenon in which the stools are malformed and watery. It is unassociated with constitutional symptoms, and there is so far no evidence that *C difficile* or its toxins play an etiologic role. Simple antibiotic-induced diarrhea is common and occurs with antibiotic therapy in 3% to 10% of adults and children, with generally a higher rate in children.

The incidence of *C difficile* colitis is not well ascertained. Several studies of outpatient populations indicate a frequency of 1 to 3 cases per 100,000 patients being treated with an oral antibiotic (Table 1).[13] The incidence in patients in hospital may be as high as 1 per 100 to 1,000 inpatients and varies by hospital, according to the patient mix. The cause of colitis is related to the reduction of certain elements of the normal fecal flora, allowing *C difficile* to find an ecologic niche; a reduced number of anaerobes is probably more important than similar effects in the aerobic flora. It is clear that several nonclostridial anaerobes play a role in restraining growth or toxigenesis, or both, of *C difficile* both in vitro and in vivo.

TABLE 1.—*Antibiotic-Related Gastrointestinal Side Effects*

Diarrhea—%	
Adults	3-10
Children	3-15
Colitis—Incidence	
Outpatients	1-3/100,000
Inpatients	1/100-1,000
Third-generation cephalosporins	1/1,000-2,000

The major cause of pseudomembranous colitis is the use of antibiotics. In my experience, ampicillin sodium, cephalosporins as a generic group, and clindamycin phosphate are the most frequent inducers; all antibiotic classes have been associated with pseudomembranous colitis, however, including even those that are effective in treating it—vancomycin hydrochloride and metronidazole hydrochloride, for example.[14] Colitis can be induced with only one or two doses of an antibiotic and can occur with intravenous, oral, and topically administered antibiotics. The tragedy is that some cases are precipitated by the use of antibiotics to treat viral syndromes or pseudoinfections, where antibacterial antibiotics play no discernible therapeutic role.

We are also now recognizing that pseudomembranous colitis can occur spontaneously without the use of antibiotics (Table 2). Pseudomembranous colitis has been described in patients with insulin-dependent diabetes mellitus, hepatic and renal failure, malnutrition, cystic fibrosis, and following upper gastrointestinal tract surgical procedures. In my experience, patients who are maintained at complete bed rest, particularly because of neurologic diseases or gastrointestinal dysautonomia, or both, are subject to spontaneous occurrences. The use of cytotoxic drug therapy such as methotrexate sodium or 5-fluorouracil can also induce pseudomembranous colitis, even when antibiotics are not being given.[12] These latter drugs have very modest to nil antibacterial activity but may create the syndrome by altering host defenses or subtly altering bacterial flora in the colon. The point is that while 99% of cases of pseudomembranous colitis are related to antibiotic use, other cofactors of induction increasingly are being recognized.

Diagnosis of Pseudomembranous Colitis

A diagnosis of pseudomembranous colitis is very dependent on the taking of an adequate history, one focusing on the taking of antibiotics and other drugs that could induce this disease. A physician also should consider other causes of inflammatory colitis, such as *Entamoeba histolytica, Strongyloides* and *Campylobacter* spp, *Staphylococcus aureus, Candida* sp, and *Mycobacterium tuberculosis.* The major assay for diagnosing pseudomembranous colitis uses cultures of tissue to detect the cytotoxin in fecal specimens rendered free of bacteria by filtration. Specific antiserum

TABLE 2.—*Factors Rendering Immunocompromised Patients at Risk for Toxic Enterocolitis*

Cystic fibrosis	Renal failure
Bed "bound"	Malnutrition
Neurologic disease	Surgical procedure
Intensive care units	Leukemia
Hepatic failure	Cancer chemotherapy

also is available to neutralize the actinomorphic changes caused by cytotoxin in these tests, which greatly increases the specificity of the results. In the experience of most investigators, 90% to 95% of patients whose feces are positive for cytotoxin have colitis as determined by visualization or colonic biopsy.[15] The latter test is the "gold standard." While patients have been described as having colitis specifically isolated to the cecum or ascending colon, this is uncommon in my experience. Almost all patients can be diagnosed by flexible sigmoidoscopy, for the descending and sigmoid colons are where the action is.[16] It is most important to do a biopsy of the colonic mucosa. Experienced gastroenterologists have proclaimed colons as being normal when viewed through a proctoscope, only to be surprised when the histopathologic evaluation reveals early colitis.

The range of lesions is extensive, from focal or granular colitis (mucositis), to diffuse erythema, to the development of plaques or extensive pseudomembranes. The pseudomembrane is composed of fibrin, bacteria, degenerating leukocytes, and epithelial cells. In addition, it is possible to visualize colitis in some patients by using tomographic scans of the abdomen or radionuclide tests such as indium-labeled leukocytes or gallium citrate Ga 67 scans, or both. These procedures are helpful in puzzling cases where the cytotoxin assays of fecal samples do not give clear-cut results.

A latex agglutination method now is available for detecting *C difficile* toxins in stool samples.[17] It appears, however, that this assay detects not only the toxins of *C difficile* but cellular components of other anaerobes frequently contained in normal stools. The frequency of positive results in known cases of pseudomembranous colitis may be only 60% to 80%, and the rate of falsely negative results is also high, making this an uncertain assay at the current time. A selective culture medium has also been developed that may detect as few as 1,000 colonies of *C difficile* per gram of wet weight of feces.[18] Fecal cultures for *C difficile* are generally used for research purposes, although one study has suggested that this test may play a collaborative role in determining clinical disease.[19] This culture may be useful, for example, in a patient who is not acutely ill—such as one who does not warrant empiric antibiotic therapy—or who has an unusual clinical presentation of colitis and is undergoing an extensive workup. I have seen patients with colitis in whom the cytotoxin assays of their stools were negative because of low titers of toxin in one or two specimens, while at the same time the fecal culture was positive. This latter test then served as the stimulus to do sigmoidoscopy or obtain additional fecal specimens for cytotoxin testing, which then were positive for *C difficile*. We often are uncertain of the reason(s) for the unclear endpoints in the cytotoxic assay sometimes obtained with specimens of feces from colitis patients. Hypotheses have included partial binding of the toxin by coproantibodies or alteration of the toxin by other microorganisms or substances, or both. This is an interesting area for further investigational pursuit.

Treating Pseudomembranous Colitis

After diagnosis, treatment of pseudomembranous colitis must begin promptly. In most clinically nontoxic patients with early pseudomembranous colitis, discontinuing the offending antibiotic or drug regimen is often sufficient. If the patient continues to have diarrhea over the next day or two or appears ill when initially diagnosed as having colitis, then antibiotic treatment should be promptly and empirically instituted to eradicate *C difficile* from the colonic flora. Because of the morbidity of colitis, any toxic patient with a potential for having pseudomembranous colitis should receive antibiotics effective against *C difficile* after a stool specimen and the other appropriate diagnostic studies are obtained. Fecal specimens can be saved for cytotoxin analysis at night by freezing—the colder the better.

Clostridium difficile has a variable sensitivity to antibiotics. In vitro, it is readily sensitive to penicillin and ampicillin, vancomycin, metronidazole, and bacitracin.[20] In the United States and other countries, there is a "neck-and-neck" race between orally administered vancomycin and metronidazole as to which is the drug of choice. Occasional isolates of *C difficile* are resistant to metronidazole, and I also have noted in some very ill patients with colitis that metronidazole appeared to work less rapidly than orally administered vancomycin.

While 500 mg of vancomycin given orally four times a day was used in some of the original studies, it is now clear that a dose of 125 mg four times a day is adequate to produce abundant and effective fecal concentrations in the colon to eradicate *C difficile*.[21] The dose of metronidazole administered orally varies between 250 mg and 500 mg three to four times a day.[22] Most patients are treated with either antibiotic for seven to ten days, recognizing that small amounts of the antibiotic are continually eliminated over several days following the cessation of therapy. In a comparative study of metronidazole versus vancomycin, they appeared equally efficacious, although the cost of metronidazole was less.[23] A course of vancomycin (given 125 mg four times a day) costs approximately $115 to $150 in California; metronidazole can be given at a quarter or less of this cost. Bacitracin administered orally also appears to be effective, but it is less readily available and is more expensive than metronidazole.[24] A recent report also describes teichoplanin as an effective oral antibiotic.[25]

Antiperistaltic drugs should be avoided because they may prolong the fecal carriage of the organism and may make a patient sicker. Corticosteroids—given either orally, parenterally, or by enema—have no role in treatment. Unfortunately, resection of the colon is sometimes required because the disease is diagnosed late after the onset of symptoms. Cholestyramine has been used in the past as a binder of the toxins (it does so in vitro) but, in my opinion, has only modest therapeutic effects.

A real dilemma is how to treat a patient with pseudomembranous colitis who cannot take any oral medications because of nasogastric suctioning, bowel diversions, or ileus. There have been scattered reports—and I have seen several such cases—of pseudomembranous colitis occurring while a patient was receiving intravenous metronidazole or vancomycin. The fecal concentrations achieved by intravenous in-

fusions of these two antibiotics are generally not adequate to eradicate *C difficile* from the colon. Some investigators state that to achieve some antibiosis in the colon of adults who cannot take oral drugs, vancomycin should be given at a daily dose of at least 2 grams intravenously. For these patients, I have recommended that vancomycin should also be given by enema, using a solution of 500 mg in 1 liter of a saline solution given by enema every eight hours with gentle pressure. If a patient cannot retain the enema, a Bardex catheter, as is employed in barium enemas, can be used. Others are experimenting with placing a long catheter into the small intestine and then infusing vancomycin in similar concentrations (500 mg per liter) at 1 to 3 ml per minute (T. Nostrant, MD, University of Michigan, oral communication, January 1989). If a patient truly is not responding to vancomycin by either of these routes, then a colostomy or cecostomy can be done and the antibiotic instilled directly into the colon. Other investigators are experimenting with the transabdominal injection of vancomycin into the colon under colonoscopic control. This therapy is controversial at this time, and it is uncertain if other antibiotics that are effective against *C difficile* in vitro, such as ciprofloxacin hydrochloride, will achieve favorable fecal concentrations when given orally or intravenously.

Isolation Considerations

Another important goal in treating pseudomembranous colitis is to restrict the organism to a specific patient. Environmental cultures done in several centers have indicated that defecation by a patient with symptomatic pseudomembranous colitis[26,27] causes a scattering of *C difficile* into the vicinity. The organism can be recovered from surfaces in the rooms of symptomatic patients, such as bedclothes, sheets, pillows, bed stands, sinks, and toilet seats, in the vicinity of where defecation occurred. This environmental shedding is notably less in patients who are carriers of this organism and have no diarrhea.

There have been outbreaks of *C difficile* occurring in clusters in specific locations within hospitals throughout the world.[28,29] Other reports suggest that the organism can settle in and cause repetitive nosocomial infections.[29,30] This anaerobe's ability to produce spores enables it to survive in a hospital environment, and measures to reduce its nosocomial effect are important.

The organism can be carried on the hands of medical personnel and on medical equipment. I have even isolated it from communal wheelchairs at our hospital. The importance of this form of possible transmission needs further study. Larson and co-workers have shown in hamsters that one colony-forming unit of *C difficile* placed into the mouth after one antibiotic dose will induce fatal colitis.[30] The use of enemas or nasogastric tubes has been implicated as a cofactor in inducing this disease in patients in hospital[28]; other causes are colonoscopy, antacids, and upper gastrointestinal operations. The spores are generally resistant to the quaternary ammoniacals or phenolics that hospitals use as general disinfectants. Only the use of alkaline glutaraldehyde or phosphate-buffered hypochlorite solutions are effective against *C difficile* spores in vitro. These agents are either carcinogenic (alkaline glutaraldehyde), so they must be contained in protected areas, or corrosive to surfaces (phosphate-buffered hypochlorite), which make them unsuitable for general decontamination of the environment.

TABLE 3.—*Treatment of Relapses in Clostridium difficile Infection*

Repeat vancomycin, 500 mg 4 times a day by mouth × 14 days
Slow taper of vancomycin over 2 to 3 months
Tyndallization with vancomycin
Antibiotic combinations
Vancomycin + metronidazole
Vancomycin + rifampin

In the setting of a cluster, or even with one patient with pseudomembranous colitis, isolation techniques that restrict stool contamination must be prescribed. All personnel having direct contact with these patients, their feces, and their immediate environment should wear a gown and gloves, and thorough hand washing must follow this contact. In settings of clusters in closed units, other measures used have included cohorting of patients and other isolation "barrier" techniques. Sometimes the prophylactic use of vancomycin or metronidazole has been prescribed for all patients housed in the area to blunt the transmission of this organism and the subsequent onset of colitis.

Relapses After Termination of Therapy

Some 10% to 14% of patients with *C difficile* infection relapse following termination of either orally administered metronidazole or vancomycin. A similar relapse rate is also seen with bacitracin. The reasons for these relapses are not known, but they appear to result from reinfection with the same organism either from remote areas of the colon that were not adequately sterilized with the antibiotic course or by reinfection from the environment. I have seen one patient who suffered relapses for two years before this microorganism was eradicated. Several approaches to treating relapses are outlined in Table 3. One of the more frequently used methods is to treat patients with the alternative antibiotic—if vancomycin was the antibiotic given initially, then metronidazole would be administered, or vice versa—with treatment generally prolonged to two weeks. If the patient has an additional relapse, some success may be obtained by using oral vancomycin at a dose of 500 mg four times a day, plus oral rifampin, 600 mg twice a day, for they are synergistic in susceptibility tests for *C difficile*.[32] Others have combined vancomycin with metronidazole, but I have no experience with the regimen. If a patient relapses following a second course of treatment, I recommend a course of vancomycin for two to three months with a slow taper in both dose and frequency of administration.[33] Tyndallization is a British approach in which vancomycin is given intermittently for two to three days, separated by a similar time period. Intermittent proctoscopy also should be done to exclude other colonic disorders such as Crohn's disease.

Another exciting approach to treating relapses is the use of biotherapy. It has been shown in hamsters that feces obtained from normal hamsters and given by enema—or nontoxigenic *C difficile* isolates given orally—can prevent induction of *C difficile* colitis following challenges of an antibiotic that ordinarily causes their death.[34] Recently investigators reported using an enema of a solution containing ten bacteria to inhibit *C difficile* relapses in six patients.[35] It appears that in vitro some strains of *Enterococcus faecalis, Escherichia coli, Saccharomyces boulardii, Clostridium beijerinckii,* and several bacteroid species *(Bacteroides ovatus,*

Bacteroides vulgatus, and *Bacteroides thetaiotaomicron)* can influence the growth of *C difficile* or its toxigenesis or both. The compounding of these organisms in a capsule for more palatable oral administration would be an important advance. Monospecific biotherapy by mouth has also been successful in a small number of patients: lactobacilli have been used to treat relapses, and *S boulardii* given concomitantly with antibiotic therapy reduces the frequency of *C difficile*-associated diarrhea.[36,37]

Summary

Thousands of cases of pseudomembranous colitis occur annually in the United States. Physicians giving antibiotics must advise patients to report any substantial diarrhea and be aware of the variety of clinical presentations of *C difficile* infection and the nuances of its treatment. The morbidity and mortality of toxic enterocolitis clearly can be reduced, but, unfortunately, patients still die of this disease. These deaths are preventable if physicians are aware of the problem. The eventual establishment of an effective toxoid—immunization is already used for another *Clostridium* species, *tetani*—and effective bacteriotherapy are exciting treatment modalities that may eventually eliminate this disease.

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