Colonic perforation and acute abdomen complicating antibiotic-associated pseudomembranous colitis

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Pseudomembranous colitis (PMC) is an acute bacterial infection of the colon that is caused by the organism *Clostridium difficile*. In most cases, PMC occurs when antibiotic therapy suppresses normal flora in the colon, which allows overgrowth of the *C difficile* bacteria. The severity of the disease can range from benign and self-limiting to fulminant (toxic megacolon). Only rarely does colonic perforation occur secondary to PMC. The authors report three cases of perforation in elderly women. Each patient was admitted in a toxic and septic condition, and, despite aggressive surgery, each patient died. The etiology, manifestations, diagnosis, and treatment of PMC also are discussed.

Pseudomembranous colitis (PMC) results from a colonic infection with the organism *Clostridium difficile*, which can overgrow in the colon when the normal flora are suppressed by antibiotic administration. There have, however, been reports of PMC occurring in patients without histories of antibiotic use.¹

While an asymptomatic carriage state of *C difficile* does exist, most patients who have this bacteria demonstrable in their fecal flora manifest PMC.² The disease can range from benign, self-limiting, mild diarrhea to severe, bloody diarrhea, cramps, and fever; it can progress further to toxic megacolon with perforation and sepsis.

The first reported case of PMC was in 1893 by Finney, who described it as a complication in a patient who had undergone gastroenterostomy. For quite a while, the etiology remained clouded. Then, in 1943, Hambre and associates demonstrated that penicillin could cause fatal hemorrhagic cecitis in guinea pigs. Soon it was shown that a variety of antibiotics could cause this lesion, and when it was seen that *Staphylococcus aureus* was cultured from the feces of patients with PMC, and that oral van-

comycin was therapeutic, the disease was termed staphylococcal enteritis.³

Later, it was shown that *S aureus* commonly overgrows in the colons of patients taking broad-spectrum antibiotics and that most of these patients do not develop PMC. This cast serious doubt on the role played by *S aureus* in PMC. In addition, it was demonstrated that this "enteritis" did not affect the entire intestinal tract, but only the colon, and that it ended abruptly at the ileocecal valve. Therefore, the disease was renamed antibiotic-associated pseudomembranous colitis.⁴

In 1975, it was shown that the disease could be passed from an infected animal to a healthy one via transrectal inoculation. The toxic substance could be filtered through a 0.02- μ filter, which suggested a toxin or microbial product as the etiologic agent, rather than the complete bacteria. It was then demonstrated that the toxin could be neutralized by *Clostridium sordellii* antitoxin, thereby suggesting a clostridial toxin. Stool culturing demonstrated *C difficile*.⁵

Most cases of pseudomembranous colitis are self-limiting or treatable with oral medications. Very rarely, the disease progresses to a fulminant state, which is characterized by toxic megacolon, perforation, and acute abdomen. A review⁶ in 1983 found only 13 cases of documented toxic megacolon. In 1984, Snooks and coworkers⁷ reported the first case of PMC presenting as perforation.

In this paper, we report three cases of pseudomembranous colitis; all three presented with acute abdomen secondary to colonic perforation. All three were admitted in extremis—toxic and septic, with acute abdominal findings. The working diagnosis in all three cases was ischemic colitis, and the actual diagnosis was not made until laparotomy.

Report of cases

Case 1

A 69-year-old woman was admitted on May 3, 1984, with complaints of fever, diarrhea, and worsening abdominal

pain. The diarrhea had been present for approximately two weeks, but it had become worse and associated with abdominal pain during the last three days.

The patient said that she had had a 10-to-15 pound weight loss over the past month. Her medical history was significant for steroid therapy for Addison's disease, hypertension, and cerebrovascular accident. She had completed a course of antibiotic therapy prior to development of her symptoms.

On physical examination, she was alert and oriented and in mild distress. The heart was regular, and the lungs were clear. The neck was supple and without masses or jugular venous distention. The abdomen was distended and tympanitic with high-pitched bowel sounds. There was guarding in the right lower quadrant, with rebound tenderness. Extremity examination was unremarkable.

Roentgenographs of the chest and abdomen were unremarkable, as were abdominal and pelvis echograms.

Laboratory results of significance included a white blood cell count of 20,000/cu mm and a differential shift of 37% band forms.

After fluid resuscitation in the intensive care unit, the patient was transferred to the operating room for laparotomy. The abdomen contained a large, free, intraperitoneal abscess, and the cecum was perforated. The cecal serosa was inflamed acutely. Resection of the right colon and ileotransverse colostomy were performed.

Postoperatively, the patient developed multiple medical problems, including respiratory failure, renal failure, and sepsis. Unresponsive to treatment, she died on May 13.

Pathologic study demonstrated classic PMC (Figs 1-3). In addition, stool specimens collected in the emergency department were positive for *C difficile* and also for toxin.

Case 2

After she was found unresponsive and diaphoretic in her nursing home, a 68-year-old woman was admitted on Aug 30, 1985. Her medical history included adrenal in-

Fig 1. Section through involved area of cecum in case 1 (hematoxylin and eosin stain, $\times 18$ magnification).

Fig 2. Enlargement of area in Fig 1 (case 1). There is extensive submucosal edema (E) and mucosal valvular congestion (hematoxylin and eosin stain, $\times 400$ magnification).

Fig 3. Site of perforation (asterisk) in case 1. There is ulceration into the submucosa, with an involved adjacent mucosal area (hematoxylin and eosin stain, $\times 18$ magnification).

sufficiency, insulin-dependent diabetes mellitus, and chronic obstructive pulmonary disease.

In the emergency department, the patient's blood pressure was 80/40 mm Hg. She had a grand mal seizure shortly after arrival. She was found to be theophylline toxic (theophylline level of 48 mg/mL; normal, 10-20), and antitoxicity treatment was begun immediately.

Once the postictal state wore off, the patient became alert but not oriented, which was her usual mental status. Examination of the heart and lungs was normal. Abdominal examination revealed multiple scars and prior operations, the natures of which were not known. There was guarding and rebound tenderness in the right lower quadrant. Rectal examination revealed no masses, while the stool specimen was heme positive.

Significant laboratory results included a white blood cell count of 23,300/cu mm, with a differential shift of 23% band forms. The hematocrit value was 31.8% and the serum potassium level was 3.1 mEq/L. Chest roentgenographs were unremarkable; abdominal films showed gastrectasia and cecal distention to 15 cm.

The patient was rapidly resuscitated with fluids in the intensive care unit and then taken to the operating room for laparotomy. Upon induction of anesthesia, she had a cardiac arrest, from which she was resuscitated successfully. During the operative procedure, the cecum was noted to be perforated and necrotic. The right colon was resected, and a terminal ileostomy and mucous fistula of the transverse colon was fashioned.

After a prolonged postoperative course complicated by severe multisystem failure, the patient died on Sept 12. Pathologic study of the specimen showed classic PMC (Fig 4).

Case 3

An 80-year-old woman was admitted on April 19, 1986, with a chief complaint of hematemesis. She had been in recent poor health, and had noted diffuse, non Case 3

An 80-year-old woman was admitted on April 19, 1986, with a chief complaint of hematemesis. She had been in recent poor health, and had noted diffuse, nondescript abdominal pain during the past few weeks. She had been hospitalized at another institution until three days prior to this admission for an ulcer of the left leg; her treatment there had included intravenous antibiotics.

The medical history included noninsulin-dependent diabetes mellitus, osteoarthritis, and peripheral vascular disease.

In the emergency department, she was alert and oriented but in moderate distress from abdominal pain. Her vital signs included blood pressure of 100/64 mm Hg, pulse rate of 88 beats per minute, and temperature of 98.6°F. The skin was diaphoretic. Her neck was supple, with vein distention. The heart was regular, and the lungs were clear but there was poor inspiratory effort.

The patient's abdomen was morbidly obese, distended, tympanic, and silent. There was guarding diffusely and rebound tenderness in both lower quadrants, although it localized more to the right. Rectal examination showed brown, heme-negative stool. The extremities were unremarkable.

Plain films of the abdomen disclosed dilatation of the large and small intestines, which was suggestive of colon obstruction. Chest films showed clear lung fields and an elevated right hemidiaphragm. No free air was seen on the chest or abdominal roentgenographs.

Laboratory studies of significance included a white blood cell count of 30,500/cu mm, with a differential count of 73% polymorphonuclear leukocytes, 13% band forms, 13% lymphocytes, and 1% monocytes. The platelet count was 717,000/cu mm. Urinalysis showed the presence of white blood cells too numerous to count.

In the intensive care unit, aggressive fluid resuscitation was begun. The tentative diagnosis was colon obstruction with perforation. Once the patient's condition stabilized, she was taken to surgery. Laparotomy disclosed a peritoneal cavity filled with pus. In addition to a free peritoneal abscess, she also had abscesses in the retroperitoneum, right subdiaphragmatic space, and prevesical space. The cecum was necrotic and perforated. There were inflammatory adhesions between contiguous loops of small bowel. The right colon was resected,

Fig 4. Section of cecum (case 2). There is disruption of the entire mucosa, with sparing only of the deep mucosal glands (arrow). The pseudomembrane (P) replacing the mucosa is readily apparent (hematoxylin and eosin stain, x 400 magnification).

and ileotransverse colostomy was performed.

The subsequent hospital course kept worsening, and the patient died on May 5. Pathologic study of the cecum was consistent with classic PMC (Figs 5 and 6).

Discussion

Etiology

PMC has been shown to be caused by any number of antibiotics. The disease first was recognized by its association with clindamycin and lincomycin use.² While clindamycin is probably the most implicated drug, Table 1^{4,7-14} lists those antibiotics specifically reported to cause PMC. It is thought that antibiotic administration leads to altered bowel homeostasis, which in turn allows *C difficile* overgrowth and then PMC.¹⁰

C difficile has been shown to produce a toxin that is responsible for the mucosal damage in PMC. This is neutralized in vitro by *C sordellii* antitoxin⁶ and is the basis for the *C difficile* titer determination, a laboratory study for confirming the presence of toxin in the feces.

Presentation

The earliest lesion in PMC is superficial necrosis of the mucosal surface, which occurs when glandular tubules secrete excessive amounts of mucus. The fibrinous exudate mixes with the excessive mucus, and these coalesce to form an extensive membrane—the membrane of PMC. As the disorder progresses, the membrane sloughs and leaves an ulcer that may penetrate the muscular coat. When examined endoscopically, the mucosa is edematous, has raised plaques, and is yellow in color.⁹ The plaques usually are 2 to 5 cm in size, but they can be confluent.¹⁵

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CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation, and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmologic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesicular bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential. Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE (piroxicam) at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress, nausea, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

* Reactions occurring in 3% to 9% of patients treated with FELDENE. Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

Special Senses: hearing impairment

Hematological: hemolytic anemia

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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Fig 5. Section of cecum (case 3). The area of maximal involvement is well demarcated from adjacent bowel. There is profound submucosal edema (E) (hematoxylin and eosin stain, x 100 magnification).

Fig 6. Enlargement of the area in Fig 5 (case 3). The mucosal section retains normal architecture, but demonstrates vascular congestion (arrow), adjacent to an area with total disruption of the mucosa (asterisk). Submucosal edema (E) again is demonstrated (hematoxylin and eosin stain, x 400 magnification).

In patients who develop toxic megacolon, pathologic study of the colon shows profound mural edema, which is thought to be caused by the toxin effect on the mucosa combined with fluid resuscitation.¹⁵ In later stages of PMC, the appearance of the bowel is similar to that of ischemic colitis. The fact that ischemic disease tends to be segmental and is not associated with the massive mural edema found in PMC aids in differentiation.¹⁵

There is a female:male ratio of 2.2:1 and a mean age of 54 years in PMC.¹² The disease can present in one of two ways: Patients who develop PMC while taking antibiotics usually manifest a self-limiting form, one that usually is responsive to discontinuation of the medication. Those who develop PMC days to weeks after the antibiotic is stopped, or while taking antibiotics with continuation of the

drug, usually manifest massive watery diarrhea, bloody stool, electrolyte imbalance, and albumin loss.⁴

Table 2 differentiates between the characteristics of early onset stools and late onset diarrhea.^{1,16} Table 3 shows the more common symptoms of PMC on presentation.¹⁷

On very rare occasions, PMC progresses to toxic megacolon and can go on to perforation. The extreme rarity of this complication is pointed out by Snooks and coworkers,⁷ who in 1984 found no reported cases in a review of 66 patients with PMC. Since then, a number of case reports^{6,7,10,15,18,19} of patients who were quite ill and receiving antibiotics who developed colonic dilatation, some of whom went on to develop perforation and fecal peritonitis, have appeared in the literature. Diagnostic criteria of toxic megacolon are "acute dilatation of all or part of the colon to a diameter greater than 6 cm with associated systemic toxicity."¹⁸ Toxic megacolon seems to occur with the same male:female ratio and mean age as uncomplicated PMC.¹²

Diagnosis

For stable patients, or for patients who have a confusing clinical picture, a variety of imaging techniques can assist in diagnosis. Plain roentgenographs obtained from patients with PMC can show mild, diffuse small bowel dilatation, thumbprinting of the colon, haustral thickening, ascites, and colonic dilatation.²⁰

When the patient is stable and no risk of perforation or toxicity exists, double-contrast barium enema can be helpful. The pseudomembranes appear as filling defects a few millimeters apart; at times, they are confluent. The mucosa appears edematous, without ulceration.⁹ Ultrasonography displays

TABLE 1. ANTIBIOTICS ASSOCIATED WITH PSEUDOMEMBRANOUS COLITIS.

Ampicillin ⁸
Cefaclor ⁴
Cefazolin ^{9,10}
Cefotaxime ¹¹
Cefoxitin ¹⁰
Cephadrine ⁷
Chloramphenicol ⁸
Clindamycin ⁸
Erythromycin ⁸
Metronidazole ²⁶
Nafcillin ⁸
Nitrofurantoin ⁸
Novobiocin ⁸
Oxacillin ¹²
Penicillin ⁸
Rifampin ¹³
Tetracycline ⁸
Trimethoprim/sulfamethoxazole (low dose) ¹⁴
Trimethoprim/sulfamethoxazole (full dose) ⁴

marked dilatation of the bowel loops with air, thickened, edematous bowel walls, and small amounts of free intraperitoneal fluid.²¹

While computed tomography (CT) is not part of a workup for diarrhea, many times PMC presents with symptoms suggestive of extracolonic disease, such as intra-abdominal abscess. If PMC is present, CT will demonstrate a thickened and edematous colon wall, and thumbprinting may be apparent.²²⁻²⁴ While gallium scanning would be of no use in the acute setting, it has been shown that it can demonstrate persistent activity in the area of PMC up to 96 hours before the clinical appearance of the disease. This could be useful in difficult cases, for follow-up, and to help diagnose relapses.²⁵

Diagnosis of PMC usually rests either on confirmation of the presence of *C difficile* in the feces (by culture or toxin assay) or on endoscopic evidence of pseudomembranes. The most commonly performed procedure to confirm the latter is rigid sigmoidoscopy. However, studies have shown that the pseudomembranes may be located above the 25-cm limit of the rigid sigmoidoscope.⁹ One study,⁴ which was undertaken to determine the significance of rectal sparing, demonstrated that 77.3% of patients with PMC had pseudomembranes within 25 cm from the anus (within the range of the rigid sigmoidoscope), 90.9% had pseudomembranes within 60 cm of the anus (within the range of the flexible sigmoidoscope), and 9.1% had pseudomembranes more than 60 cm from the anus (only within the range of the colonoscope). These findings suggest that if sigmoidoscopy is negative and the clinical suspicion points to PMC, the physician should proceed with colonoscopy or culture or toxin titer tests.

Using selective medium (cycloserine cefoxitin fructose agar), *C difficile* can be cultured. The absence of organisms would be a reliable negative result.² However, the presence of *C difficile* bacteria in culture does not confirm the presence of PMC, because there are rare patients who harbor the organism as asymptomatic carriers.⁸ Therefore, it is considered more reliable to perform the *C difficile* toxin assay as definitive proof of PMC.

Treatment

Successful PMC therapy involves eradication of the *C difficile* organism from the colon with antibiotics, and, secondarily, binding of the toxin using anion exchange resins. If the bacterium is killed but the toxin remains, the disease will continue. The therapy for uncomplicated^{4,26} and recurrent PMC^{27,28} is outlined in Table 4.

Vancomycin is the mainstay of antibiotic therapy. It is generally used at a dose of 500 to 2,000

mg daily in four divided oral doses.^{4,26} When the patient's condition prohibits oral medication, vancomycin can be delivered as a retention enema in a dosage of 1 g/1,000 cc of saline solution every 6 h.²⁹ This drug is effective against all strains of *C difficile* and attains fecal levels of 25 to 200 times its minimum inhibitory concentration (MIC). The drug of second choice is metronidazole⁴. The regimen is 1.2 to 1.5 g/day in divided oral doses.²⁶ Unfortunately, there have been case reports of this agent causing PMC; also, it is well absorbed in the small bowel, which leads to questionable fecal levels.²⁶ Finally, bacitracin has been used for PMC, with a dosage of 25,000 units four times a day.²⁶

The anion exchange resins used for the treatment of PMC are cholestyramine³⁰ and cholestipol.¹⁷ These reversibly bind the *C difficile* toxin; either is given at a dose of 4 g orally three times daily.⁴ Antiperistaltic agents should not be used, because they can worsen or prolong the course of the disease.²⁶

While vancomycin is almost always successful in treating PMC, recurrence rates as high as 14% have been reported.²⁷ The two possible etiologies of recurrence are spore formation by the *C difficile* organism and environmental reinfection.²⁷ Various regimens have been suggested to treat these relapses. These range from a five-week course of oral vancomycin³⁰ to a prolonged course of cholestyramine³⁰ to a tapering dosage schedule of vancomycin and cholestipol.²⁷

Because of the possibility of environmental cross-contamination, patients with PMC should be isolated. Contamination can come from hospital personnel or inanimate objects. The organism can survive on a hospital floor for up to five months.³¹

Once pseudomembranous colitis progresses to

TABLE 2. CHARACTERISTICS OF STOOLS OF 40 PMC PATIENTS (ADAPTED FROM MILLER AND ASSOCIATES).¹⁶

Parameter	Early onset	Late onset
No. of patients	34	6
No. of stools/day	>5	>5
Stool consistency	Watery	Soft, bulky
Mucus in stool	30	6
Blood in stool	4	0

TABLE 3. CLINICAL FEATURES OF PMC (ADAPTED FROM TEDESCO).¹⁷

Presentation	Frequency (%)
Water diarrhea	90-95
Bloody diarrhea	5-10
Crampy abdominal pain	80-90
Fever (100° F-104° F)	80
Leukocytosis	80
Rebound tenderness	10-20

TABLE 4. PMC THERAPY.

Agent	Dosage	Route
Uncomplicated PMC		
Antibiotics ^{4, 26}		
Vancomycin	500-2,000 mg/day	oral, ¹⁶ enema ²⁹
Metronidazole	1.2-1.5 g/day	oral
Bacitracin	25,000 units four times daily	oral
Anion exchange resins ¹⁹		
Cholestyramine	4 g three times daily	oral
Cholestipol	4 g three times daily	oral
Recurrent PMC		
Schedule 1 ²⁹		
Vancomycin 125 mg every 6 h for seven days, or		
Vancomycin 125 mg daily plus cholestipol 5 g every 12 h for five to seven days, or		
Vancomycin 125 mg plus cholestipol 5 g every 12 h for five to seven days, or		
Cholestipol 5 gm every 12 h for 14 days		
Schedule 2 ³⁰		
Vancomycin 125 mg every 6 h for seven days, or		
Vancomycin 125 mg every 12 h for seven days, or		
Vancomycin 125 mg once daily for seven days, or		
Vancomycin 125 mg every other day for seven days, or		
Vancomycin 125 mg every third day for 14 days		

the point of perforation and acute abdomen, aggressive surgical management is indicated. Our three patients died as a result of colonic perforation with resultant sepsis and multisystem failure. If an aggressive surgical management posture is undertaken and patients are seen prior to perforation, perhaps the outcome can be improved.

Summary

Pseudomembranous colitis occurs when there is a bacterial overgrowth of *C. difficile* in the colon, usually, but not always, from antibiotic use. The severity of the disease can range from mild, self-limited diarrhea to fulminant toxic megacolon with perforation, and the treatment can vary from simple discontinuation of the offending antibiotic to colon resection for perforation. We reported three patients who presented with colonic perforation secondary to PMC and described the diagnosis and treatment and recurrent PMC.

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Clinically effective in serious polymicrobial infections involving *Bacteroides fragilis* and other important anaerobes, staphylococci, streptococci, and pneumococci. Follow-up therapy to CLEOCIN IV, or initial therapy when clinically appropriate.

Positive penetration profile. CLEOCIN HCl is rapidly and predictably absorbed, rapidly penetrates most body tissues and fluids, including bone and pus. Food does not significantly affect absorption.

Not a beta-lactam. No cross-allergenicity with penicillins or cephalosporins. However, maculopapular rash and urticaria have been observed during therapy with CLEOCIN.

CLEOCIN is generally well tolerated. Like many other antibiotics, however, it has been associated with *Clostridium difficile* colitis. Available evidence does not suggest a relationship to dosage or route of administration.

NEW
Cleocin HCl[®] 300 CAPSULES
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Cleocin HCl[®] 300 mg CAPSULES

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CLEOCIN PHOSPHATE[®] Sterile Solution
CLEOCIN HCl[®] Capsules
(clindamycin)

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic associated colitis.

Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dose is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

INDICATIONS

Serious infections caused by susceptible anaerobic bacteria. Patients with serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci in whom its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin). Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

CONTRAINDICATIONS

History of hypersensitivity to clindamycin or lincomycin.

WARNINGS

See WARNING box. A toxin produced by *Clostridia* is one primary cause of antibiotic

associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Vancomycin has been found to be effective in the treatment of antibiotic associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in 3 or 4 divided doses for 7 to 10 days. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. *Usage in Pregnancy:* Safety has not been established. *Usage in Newborns and Infants:* Appropriate monitoring of organ system functions is desirable. CLEOCIN PHOSPHATE contains benzyl alcohol which has been associated with a fatal gasping syndrome in infants. *Nursing Mothers:* Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 mcg/ml. *Usage in Meningitis:* Since clindamycin does not diffuse adequately into the cerebrospinal fluid, it should not be used to treat meningitis.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

Older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis and also in atopic individuals. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal and/or hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

During prolonged therapy, periodic liver, and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Clindamycin has neuromuscular blocking properties and may enhance other neuromuscular blocking agents. Use with caution in patients receiving such agents. Do not inject clindamycin IV undiluted as a bolus. Dilute prior to IV administration to 300 mg per 50 ml or more of diluent. Infuse over at least 10-60 minutes. (See Dosage and Administration.) CLEOCIN HCl Capsules 75 mg and 150 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals,

especially in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Gastrointestinal: Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) An unpleasant or metallic taste has been reported with high doses.

Hypersensitivity Reactions: Maculopapular rash and urticaria. Generalized mild to moderate morbilliform-like skin rashes are the most frequent adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been reported. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents should be available for emergency treatment. **Liver:** Jaundice and abnormalities in liver function tests have been observed.

Hematopoietic: Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made.

Local Reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. **Musculoskeletal:** Rare instances of polyarthritides have been reported. **Cardiovascular:** Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid IV infusion. (See Dosage and Administration.) **Renal:** Renal dysfunction with azotemia, oliguria, proteinuria has rarely been observed. No direct relationship has been established.

DIRECTIONS FOR DISPENSING

Pharmacy Bulk Package—Not for Direct Infusion The Pharmacy Bulk Package is for use in a Pharmacy Admixure Service only under a laminar flow hood. Entry into the vial should be made with a small diameter sterile transfer set or other small diameter sterile dispensing device, and contents dispensed in aliquots using aseptic technique. Multiple entries with a needle and syringe are not recommended. AFTER ENTRY USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED WITHIN 24 HOURS AFTER INITIAL ENTRY.

HOW SUPPLIED

Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Vials of 2, 4, and 6 ml.

Vials of 600 mg and 900 mg are available in ADD-Vantage[™] Vial system.

1-60 ml Pharmacy Bulk Package.

CLEOCIN HCl as 75 mg, 150 mg, and 300 mg capsules.

Caution: Federal law prohibits dispensing without prescription.

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For additional product information see your Upjohn representative.

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