Patterns and Prognosis of *Clostridium difficile* Colitis

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The incidence of *Clostridium difficile* colitis has increased during recent years, presumably because of liberal use of broad-spectrum antibiotic regimens. METHODS: A retrospective review to determine patterns of *C. difficile* colitis development, morbidity, and treatment results was undertaken. During an 18-month period, 90 patients were diagnosed with *C. difficile* colitis by fecal toxin assays. Patient demographics, symptoms, previously administered antibiotic regimens, diagnostic evaluations, treatment modalities, morbidity, and mortality were identified, entered into a computer data base, and analyzed. RESULTS: The mean age was 58 years; males outnumbered females 1.2:1. Among 90 patients, 41 (46 percent) developed *C. difficile* colitis after surgical procedures. Eighty (89 percent) patients received antibiotic therapy before developing *C. difficile* colitis: 35 (44 percent) for documented infections and 45 (56 percent) as empiric or prophylactic therapy. Cephalosporins, penicillins, quinolones, vancomycin, and aminoglycosides were the most frequently administered antibiotic classes prior to *C. difficile* colitis diagnosis. Ten (11 percent) patients developed *C. difficile* colitis without previous antibiotic therapy. Eighty-two (91 percent) patients presented with diarrhea, while eight (9 percent) had fever only. Primary *C. difficile* colitis treatment for both groups included vancomycin (66 percent), metronidazole (24 percent), or both drugs (10 percent). Ten (11 percent) patients received no treatment. No patient developed toxic colitis or megacolon. Colonoscopy was performed in four (4 percent) patients; pseudomembranes were identified in one (25 percent) patient. There was one *C. difficile* colitis recurrence after treatment, but no *C. difficile* colitis-associated morbidity. Mortality (14 patients, 16 percent) was not related to *C. difficile* colitis, but to underlying illness. No difference in patient age, sex, previous antibiotic administration, serum albumin, total days hospitalized, duration of *C. difficile* colitis antibiotic therapy, *C. difficile* colitis treatment regimens, or mortality was identified between nonsurgical and surgical patients. The white blood cell count was significantly lower in the nonsurgical group however. *Clostridium difficile* colitis developed most commonly after antibiotic administration with symptoms of diarrhea, but did occur without previous antibiotic administration or diarrhea. CONCLUSION: Despite the clinical setting, *C. difficile* colitis had no associated morbidity and treatment was highly effective. Mortality was related to underlying medical illness, not *C. difficile* colitis. [Key words: *Clostridium difficile* colitis; Diarrhea; Immunosuppression]

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The incidence of *Clostridium difficile* colitis (CDC) has increased during recent years, presumably because of more liberal use of broad-spectrum antibiotic regimens. Profuse watery diarrhea and cramping abdominal pain are the hallmark symptoms of this disorder. If left untreated, severe dehydration, electrolyte disorders, hypoalbuminemia, toxic megacolon, colonic perforation, or death may result. The diagnosis of CDC can be made by endoscopic evaluation, fecal cultures, or fecal toxin assays. Once the diagnosis has been established, treatment involves supportive measures, discontinuation of precipitating antibiotic regimens, and the administration of enteral antibiotic therapy specific for CDC.

Historically, the development of CDC has been associated with hospitalized patients receiving antibiotic therapy. Recently, we have observed a growing number of patients who have developed CDC outside of the hospital setting, without previous antibiotic administration, and following subtotal colectomy. Many of these patients have received multimodality treatment for neoplastic disorders, including surgical extirpation, chemotherapy, and radiation therapy. In these patients, immunocompromise may be the most significant predisposing factor associated with the develop-

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ment of CDC. With new advances in the treatment of neoplastic disorders and the increasing incidence of the human immunodeficiency virus, an increase in the number of immunocompromised patients can be expected. As a result, the growing trend of developing CDC in nonhospitalized patients or patients without previous antibiotic exposure may be expected to continue.

The purpose of this study was to examine the experience of CDC at a tertiary care medical facility. The pathogenesis of this disorder was evaluated, including antibiotics presumed to have a role in the development of CDC. Patient demographics, methods of diagnosis including the role of colonoscopy, and different therapeutic regimens and their outcomes were also evaluated. Finally, a comparison of the differences and similarities between patients undergoing major surgical procedures and those being treated for nonsurgical conditions was conducted.

MATERIALS AND METHODS

A computer search of the Department of Infectious Disease Registry at the St. Louis University Hospital during an 18-month period was undertaken. All patients identified with positive fecal cytotoxin assays for *C. difficile* were included in this study.

The medical records of the patients diagnosed with CDC were then reviewed and the following data obtained: age; gender; admission diagnosis; antibiotic administration before the development of CDC, including antibiotic class, duration of administration, and reason for administration (prophylactic, empiric, therapeutic); presenting symptoms; white blood cell count; serum albumin; results of colonoscopic evaluation; treatment regimen, including antibiotic type and duration; duration of hospitalization; morbidity; mortality; and performance of major surgical procedures.

The data were entered into a computer data base and the patients undergoing major surgical procedures were compared with those being treated for nonsurgical conditions. Statistical analysis for discrete variables was accomplished utilizing a chi-squared test, while continuous variables were analyzed using an unpaired Student's *t*-test; *P* values of less than 0.05 were considered significant.

RESULTS

Over an 18-month period from 1990 to 1992, 90 patients were diagnosed with CDC. There were 49 males and 41 females. The average age was 58 (range, 17–92) years. The average duration of hospitalization was 34 days, with a range of 5 to 120 days.

Eighty-four (93 percent) patients had been hospitalized for varying lengths of time and with varying degrees of illness prior to the diagnosis of CDC, while six (7 percent) patients in this series developed symptoms of CDC outside of the hospital and were diagnosed upon hospitalization. One of these patients had been treated previously with metronidazole for CDC with resolution of her symptoms, and was the only patient to have a recurrence of CDC. The other five patients had associated pancreatic pathology (two patients) or malignancies in various stages of treatment (three patients) (Table 1).

Eighty (89 percent) patients had received antibiotic therapy before the development of CDC: 35 (44 percent) for documented infections and 45 (56 percent) as part of empiric or prophylactic therapy. Thirty-five patients were treated with single antibiotic regimens, 13 with single agents, and 22 with multiple agents, while 45 patients were treated with multiple antibiotic regimens prior to the development of CDC. Cephalosporins, penicillins, quinolones, vancomycin, and aminoglycosides were the most frequently administered antibiotic classes in patients who developed CDC (Table 2).

Ten (11 percent) patients developed CDC without previous antibiotic therapy. This group of patients included the six patients who developed CDC outside of the hospital setting. The associated admission diagnoses of the other four hospitalized patients included sickle-cell crisis, breast cancer, gastrointestinal tract hemorrhage, and FK506 toxicity following liver transplantation.

Watery diarrhea was the initial presenting symp-

Table 1.
Associated Diagnosis of Patients Developing *C. difficile* Colitis Outside the Hospital Setting

Pancreatic pseudocyst
Acute pancreatitis
Acute myelogenous leukemia
Chronic myelogenous leukemia
Status post bone marrow transplant
Esophageal cancer
Status postesophagogastrectomy
Rectovaginal fistula*
Status postendorectal advancement flap with diverting colostomy

* Probable recurrence of CDC.

Table 2.
Antibiotics Used Before Development of *C. difficile* Colitis

	Single Agent/Single Regimen (n = 13)	Multiple Agents/Single Regimen (n = 22)	Multiple Agents/Multiple Regimen (n = 45)
Cephalosporin	7	16	47
Penicillin	3	2	25
Quinolone	2	5	11
Macrolide	0	2	1
Vancomycin	0	12	21
Clindamycin	0	3	7
Metronidazole	0	4	5
Imipenem	1	1	4
Aztreanam	0	2	6
Doxycycline	0	1	0
Trimethoprim/sulfamethoxazole	0	1	10
Aminoglycoside	0	3	15

tom in 82 (91 percent) patients, whereas fever was the presenting symptom in the remaining eight (9 percent) patients. Leukocytosis (white blood cell count $>10.5 \times 10^3/ml^3$) was present in 41 (46 percent) patients but, as a result of concurrent infectious processes in many patients, was difficult to solely attribute to CDC. The average white blood cell count was $12.8 \times 10^3/ml^3$ with a range of 0.1 to $61.1 \times 10^3/ml^3$.

The diagnosis of CDC was made by positive latex agglutination fecal cytotoxin assays in all 90 patients. Four (4.4 percent) patients underwent colonoscopic evaluation, but only one (25 percent) patient was found to have pseudomembranes.

Once the diagnosis of CDC was established, supportive therapy was initiated, with emphasis on intravenous fluid resuscitation and electrolyte replacement. Cessation of precipitating antibiotic regimens was accomplished when possible, and enteral antibiotic therapy specific for *C. difficile* was instituted. Fifty-three (59 percent) patients were treated with vancomycin, 19 (21 percent) patients with metronidazole, and 8 (9 percent) patients with sequential vancomycin and metronidazole. The average duration of treatment was nine days, with a range of 1 to 16 days. Ten (11 percent) patients had resolution of their symptoms without *C. difficile*-specific antibiotic therapy. A comparison of the therapeutic antibiotic intervention used for the patients who underwent major surgical procedures and those who were treated for nonsurgical conditions is presented in Table 3.

Forty-one (46 percent) patients had developed CDC following major surgical procedures, most commonly gastrointestinal or orthopedic procedures. The distribution of surgical procedures are presented in Table 4.

A comparison of the demographic features of the patients undergoing major surgical procedures and those treated for nonsurgical conditions is presented in Table 5. There was no significant difference between the groups, except for the white blood cell count, which was significantly lower in the nonsurgical group, probably secondary to the number of neutropenic patients receiving chemotherapy. In the nonsurgical group, 13 (27 percent) patients had white blood cell counts less than the established normal range ($4.5 \times 10^3/ml^3$) compared with one (2 percent) patient in the surgical group of patients.

Only one (1 percent) patient had a recurrence of CDC following treatment with metronidazole. Successful treatment of the recurrence was accomplished with a course of vancomycin.

Table 3.
Therapeutic Intervention

	Nonsurgical Group (n = 49)	Surgical Group (n = 41)
Vancomycin	24 (49%)	29 (71%)
Metronidazole	14 (29%)	5 (12%)
Sequential vancomycin and metronidazole	7 (14%)	1 (2)
No antibiotic therapy	4 (8%)	6 (15%)

Table 4.
Distribution of Surgical Procedures Performed

Surgical Class	No.
Cardiovascular	2
Gastrointestinal	12
Genitourinary	1
Gynecologic	1
Orthopedic	7
Peripheral vascular	3
Plastic	4
Solid organ transplantation	2
Thoracic	3
Miscellaneous	6

There was no significant morbidity (toxic megacolon, colonic perforation) associated with CDC. There were 14 (16 percent) deaths in this series, but these were related to the patient's underlying medical illness in each instance and not to CDC (Table 6).

Table 6.
Cause of Death

Sepsis	3
Cardiac failure	4
Respiratory failure	3
Multisystem organ failure	4

DISCUSSION

CDC was first described in 1893.[1] The etiology of this disease process remained obscure until a toxin was isolated from a patient with documented pseudomembranous colitis in 1977.[2] Subsequent studies[3, 4] demonstrated this toxin was produced by *C. difficile*, a gram-positive anaerobic bacillus first described in 1935.[5]

Clostridium difficile is an uncommon inhabitant of the colon in healthy adults, being isolated in the feces of less than 5 percent of those studied.[6-8] In infants and neonates, however, the incidence may approach 50 percent.[9-12] Toxigenic strains of *C. difficile* account for approximately 75 percent of all isolates identified and are responsible for the production of two different toxins—A, an enterotoxin and B, a cytotoxin.[13] Although their mechanism of action is not clearly defined, the toxins are involved in the disruption of cellular membranes, microfilaments, and protein synthesis.[7]

CDC has been associated with several etiologic factors, including colonic stasis and antibiotic usage.[6, 14-17] Colonic stasis is associated with changes in the normal colonic flora, increased mucosal absorption of the *C. difficile* toxins, and inflammatory mucosal changes.[18, 19] Antibiotic therapy (enteral, parenteral, or topical), particularly broad-spectrum antibiotic therapy, may alter normal colonic flora and permit overgrowth of *C. difficile* in the colon.[6, 7, 20, 21] The most frequently implicated antibiotics include cephalosporins, penicillins, and clindamycin.[17, 21] Eighty-nine percent of the patients in this study had received antibiotics before the development of CDC. Cephalosporins, penicillins, quinolones, vancomycin, and aminoglycosides were the most frequently administered antibiotic classes in this series. Unlike other studies[17, 21] clindamycin was not found to be widely used in this study prior to the development of CDC.

Impairment of the normal immunologic defense mechanisms may be more important in the development of CDC than colonic stasis or antibiotic

Table 5.
Comparison of Nonsurgical and Surgical Patients

	Nonsurgical Group (n = 49)	Surgical Group (n = 41)	*P*
Age (yr)	57.7 ± 2.6	58.6 ± 3.4	NS*
Male	23	26	NS†
Previous antibiotic therapy	45	35	NS†
Albumin (g/dl)	2.9 ± 0.1	3.0 ± 0.1	NS*
White blood cell count ($\times 10^3/ml^3$)	10.5 ± 1.6	15.6 ± 1.8	0.03*
CDC antibiotic therapy (days)	9.6 ± 0.5	8.3 ± 0.5	NS*
Hospitalization (days)	31.1 ± 3.8	37.5 ± 4.1	NS*
Mortality	8	6	NS†

Values expressed as mean ± standard error of the mean. NS = not statistically significant.
* *t*-test.
† Chi-squared test.

administration. Adequate nutritional status is important in the maintenance of an intact immunologic system. The average albumin in this series was 3.0 g/dl, with a range of 1.6 to 4.6 g/dl. This was less than the normal range (3.7–5.0 g/dl), suggesting mild nutritional depletion. Seven (8 percent) patients in this series had undergone solid organ transplantation (kidney, liver, pancreas) and were being treated with various immunosuppressive regimens to prevent rejection of the transplanted organs. One (1 percent) patient had documented human immunodeficiency syndrome, with impairment of immune function. Twenty-five (28 percent) other patients were in various stages of treatment for different neoplastic disorders. Treatment modalities included surgical extirpation, chemotherapy, and radiation therapy. Bone marrow transplantation had been performed in several patients when indicated. Immune dysfunction may be associated with neoplastic disorders, and is exacerbated with chemotherapy and radiation therapy. Although no quantitative evaluation of patient immunologic function was undertaken, this may prove to be an area of future research interest in the pathogenesis of CDC.

The symptoms associated with CDC include profuse watery diarrhea and cramping abdominal pain.[6, 7, 14–17, 22, 23] As in these studies, diarrhea was the most common symptom associated with CDC. Fever, leukocytosis, and hypoalbuminemia were also common findings.[6, 7, 14, 15, 17, 22] If left untreated, dehydration, hypovolemia, toxic megacolon, colonic perforation, hemorrhage, and death may result.[6, 7, 14] Variation in white blood cell counts may not be reliably related to CDC though, as it may be a result of associated infectious processes, underlying medical conditions (malignancy), and treatment modalities (chemotherapy, steroids).[15] Infectious processes and steroids may result in leukocytosis, while chemotherapy may result in leukopenia. A number of patients in the nonsurgical group were being treated with chemotherapy for malignancies, resulting in white blood cell counts as low as $0.1 \times 10.^3/ml^3$.

The diagnosis of CDC can be established by endoscopy, fecal cultures, or fecal cytotoxin assays. Endoscopic evaluation is highly sensitive and the diagnosis can be made by the presence of white pseudomembranes,[7, 14, 17] often in association with edematous, friable mucosa.[24] The presence of pseudomembranes, however, was only demonstrated in 14 percent of those undergoing colonoscopy in one study.[15] Because of the reliability of the cytotoxin assay at our institution, colonoscopy is not routinely performed. Only one (25 percent) patient was found to have pseudomembranes on endoscopic examination. Since pseudomembranes are not present in all cases of CDC, histologic evaluation may prove useful in establishing the diagnosis.[14,17] Typical histologic features involving inflammatory mucosal changes are frequently identified in specimens obtained from the pseudomembranes, but are not usually identified in specimens obtained from unaffected segments.[6] Fecal cultures in selective media can provide the definitive diagnosis, but lack specificity and may take several days to grow. The cytotoxin assay is currently the most widely used diagnostic modality because of the rapidity and availability of the test. Detection of toxin B is the "gold standard," but few laboratories have the necessary facilities for the tissue culture assays and it takes up to 24 hours before the results are available. A commercially available latex particle agglutination assay is easily performed, but is not as specific and detects toxin A and another biologically inactive protein product of *C. difficile*. A third test detects toxin A. This enzyme immunoassay is the preferred alternative to the toxin B detection test.[7, 21]

False negative results have been reported for both fecal cultures and cytotoxin assays, and performance of both tests has been recommended.[15] False negative results may be attributed to technical factors (specimen collection, storage, or testing) or variation of the characteristics of the different strains of *C. difficile*.[15, 21]

The treatment of CDC includes supportive measures, elimination of the underlying process, and treatment of the bacterial contamination. Intravenous fluid therapy and electrolyte replacement are important.[17] Utilizing supportive measures alone will result in clinical improvement within several days in about 25 percent of all patients.[25] If the etiology is antibiotic-related, discontinuation of the precipitating antibiotic regimen should be undertaken.[7, 21] This may not be possible, however, because the antibiotics may be necessary for the treatment of associated infectious processes. In this series, 10 (11 percent) patients had resolution of the CDC with supportive measures alone.

Patients who are refractory to supportive measures or critically ill should be treated with antibi-

otic therapy specific for *C. difficile*. Enteral antibiotic therapy is preferential to parenteral antibiotic therapy since *C. difficile* remains within the lumen of the colon, seldom invading the colonic mucosa. Enteral vancomycin is the preferred antibiotic regimen because *C. difficile* is highly sensitive to this drug.[14, 20, 22] Intravenous vancomycin is not as efficacious, since therapeutic concentrations within the lumen of the intestines are difficult to attain.[7] Vancomycin dosage ranges from 125 mg to 500 mg four times a day for 5 to 14 days.[15, 21] Metronidazole and bacitracin are also effective in the treatment of *C. difficile*, but not all isolates of this organism are sensitive to the antibiotics. Furthermore, enteral metronidazole is readily absorbed from the small intestines, making therapeutic intraluminal colonic levels difficult to attain. Enteral metronidazole may, however, be preferential to enteral vancomycin because of its significantly lower cost.[26] A metronidazole dosage of 500 mg two times a day for 7 to 14 days is recommended.[21] A bacitracin dosage of 500 mg four times a day for 7 to 14 days is also recommended.[7]

Vancomycin or metronidazole was used to treat patients with CDC in this series. Eight patients were initially treated with one agent or the other, and changed to the other agent in the middle of therapy because of failure of improvement of symptoms. No morbidity or mortality was associated with the ten patients who did not receive *C. difficile*-specific antibiotic therapy, with complete resolution of their symptoms. A summary of our treatment algorithm for patients with diarrhea is presented in Figure 1.

With the administration of enteral antibiotic therapy, improvement in symptoms is typically noted within one to five days.[7, 26] Even after cessation of toxin production, inflammatory changes may persist and result in prolonged fever and diarrhea.[7]

Pharmacologic agents with antiperistaltic activity (codeine, diphenoxylate, atropine, loperamide) have been evaluated, but are not widely used because of concerns of colonic stasis, toxin retention, and the development of toxic megacolon.[7, 15]

Cholestyramine has also been evaluated in the treatment of mild CDC attributable to its ability to

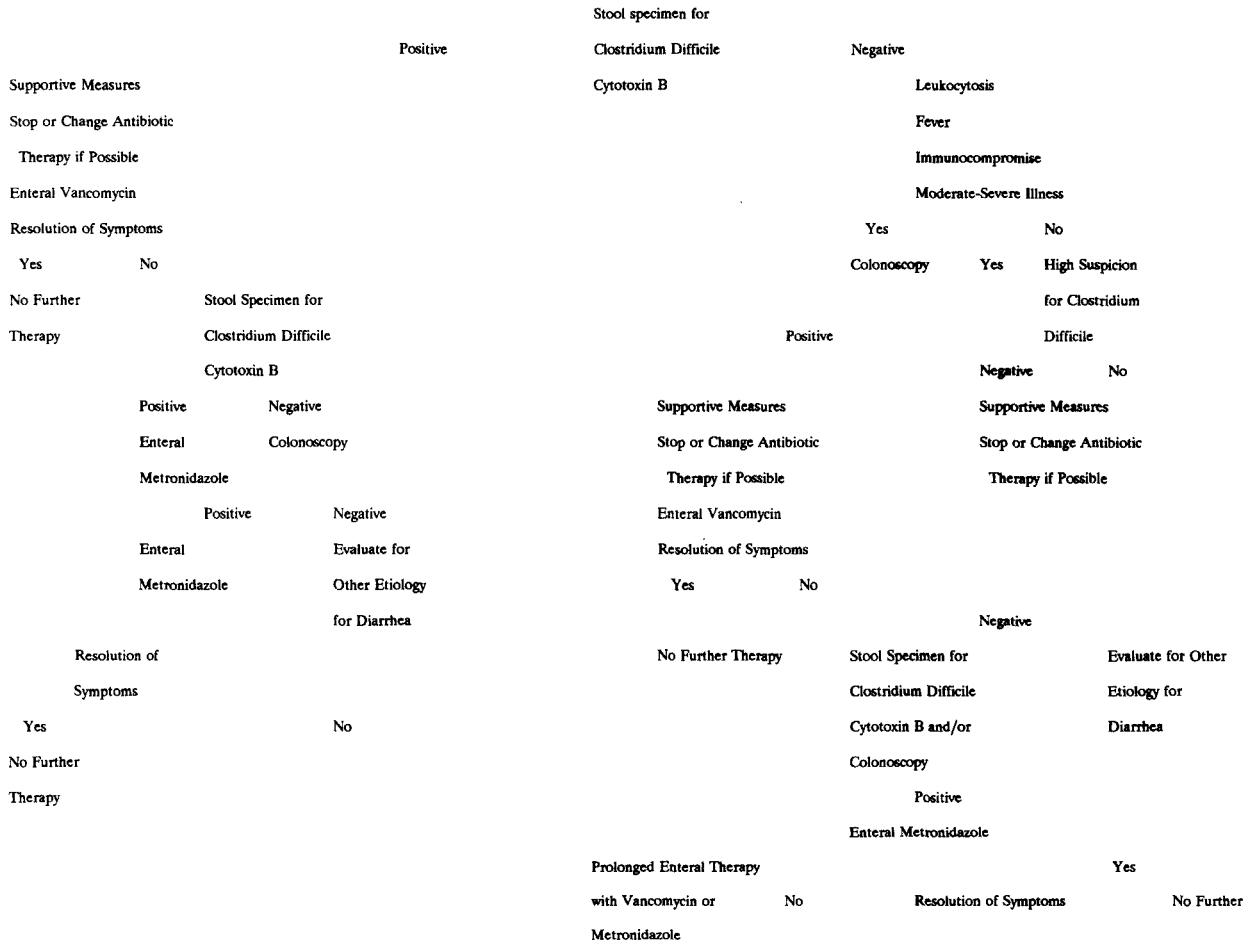

Figure 1. Algorithm for evaluation and management of diarrhea.

bind the toxin.[7, 27] However, it is not recommended in severe cases of CDC because it is not as effective as specific antimicrobial therapy.[7]

Relapses of CDC typically occur from one to four weeks after the cessation of treatment. Recurrence is postulated to occur from either germination of vegetative *C. difficile* spores persisting through treatment or from recolonization of the colon through human or environmental contacts.[7,28,29] Relapses after treatment with enteral vancomycin or metronidazole have been reported to be as high as 20 percent[15, 30] and 15 percent,[15, 26] respectively. Retreatment with vancomycin or metronidazole at the above dosages is recommended after early detection of relapses.[7] Only one patient is this study (previous endorectal advancement flap and diverting colostomy for rectovaginal fistula) had recurrence of CDC following initial treatment with metronidazole. Successful treatment of the recurrence was accomplished with a course of vancomycin.

CDC has been associated with a high incidence of morbidity and mortality in the past. Complications, including dehydration, electrolyte imbalances, and colonic perforation, have significantly declined in recent years. In this series, aggressive fluid and electrolyte resuscitation were emphasized. Routine radiologic surveillance of the abdomen was performed when indicated for colonic distention. As a result, there were no cases of toxic megacolon or colonic perforation in this study. The incidence of mortality associated with CDC has also been declining in recent years, probably attributable to early diagnosis and aggressive intervention. In this series, mortality in all instances was attributable to underlying medical conditions and not to CDC.

A comparison of several large series of CDC is presented in Table 7. The mean age and male to female ratio were similar in these series, except for the series by Gerding *et al.*[33] where 99 percent of the patients were male. Previous antibiotic administration was reported in the majority of the patients in all of the series, and diarrhea was the single most common presenting symptom. Treatment of CDC with antibiotics specific for *C. difficile* was variable, ranging from 24 percent to 100 percent of the patients studied. Recurrence rates following antibiotic treatment for CDC were less than 10 percent, except for the study by Talbot *et al.*[34] (17 percent). Mortality ranged from 3 percent to 27 percent and was almost always related to underlying disease processes and not to CDC.

Table 7.
Series Comparison of *C. difficile* Colitis

Author	Year Published	No. of Patients with CDC	Mean Age (yr)	Males (%)	Previous Antibiotic Administration (%)	Previous Surgical Procedure (%)	Diarrhea as Presenting Symptom (%)	Treatment with CDC-Specific Antibiotic (%)	Recurrence (%)	Mortality (%)
Mogg *et al.*[14]	1979	66	59	28 (42)	66 (100)	56 (85)	64 (97)	16 (24)	NR	18 (27)
Rocca *et al.*[31]	1984	34	61	13 (38)	34 (100)	NR	34 (100)	14 (41)	1 (3)	5 (15)
Rosenberg *et al.*[32]	1984	75	68	33 (44)	75 (100)	75 (100)	75 (100)	53 (71)	6 (8)	2 (3)
Church *et al.*[15]	1986	133	57	65 (49)	125 (94)	51 (38)	121 (91)	68 (51)	10 (8)	31 (23)
Gerding *et al.*[33]	1986	109	64	108 (99)	100 (92)	84 (77)	109 (100)	NR	NR	NR
Talbot *et al.*[34]	1986	190	NR	83 (44)*	151 (79)	108 (57)	188 (99)	144 (76)	32 (17)	NR
Clarke *et al.*[35]	1990	25	55	15 (60)	24 (96)	NR	25 (100)	25 (100)	1 (4)	1 (4)
Present study	1993	90	58	49 (61)	80 (89)	41 (46)	82 (91)	80 (89)	1 (1)	14 (16)

NR = not reported.
* Sex of 16 children not reported.

CONCLUSION

The development of CDC is closely associated with the administration of broad-spectrum antibiotic regimens. Cephalosporins, penicillins, quinolones, vancomycin, and aminoglycosides were the most frequently administered antibiotics prior to the development of CDC in this series. Immunologic dysfunction may also be an important risk factor in the development of CDC, as a significant number of patients in this series had neoplastic disorders, or had undergone solid organ transplantation with subsequent need for pharmacologic immunosuppressive regimens. Diarrhea was the most frequent symptom, and the diagnosis in all cases was established with a cytotoxin assay. Treatment, including supportive measures and enteral vancomycin or metronidazole, was successful in treating CDC, with only one recurrence. A comparison of patients undergoing surgical procedures with those being treated for nonsurgical conditions failed to demonstrate differences in age, duration of hospitalization, sex, previous antibiotic therapy, serum albumin levels, CDC antibiotic therapy duration, or mortality. The white blood cell count was significantly less in the nonsurgical group because of the number of neutropenic patients in that group receiving chemotherapy. Finally, there was no significant morbidity associated with CDC, and all deaths in this series were related to underlying medical conditions, not to CDC.

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