MAJOR ARTICLE

Adjunctive Intracolonic Vancomycin for Severe *Clostridium difficile* Colitis: Case Series and Review of the Literature

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Successful treatment of severe *Clostridium difficile* colitis has been reported with the use of adjunctive intracolonic vancomycin (ICV) therapy. We report a descriptive case series and review the literature on patients with *C. difficile* colitis who received adjunctive ICV therapy. Nine patients received antibiotics within 6 weeks prior to presentation. Complete resolution of the clinical presentation occurred in 8 patients (88.9%), and eradication of *C. difficile* cytotoxin production was documented in 3 (75%) of 4 patients who were tested after the completion of adjunctive ICV therapy. One patient (11.1%) died as a result of progressive multisystem organ failure. In the 6 weeks after the completion of treatment for *C. difficile* colitis, no patient had recurrent disease, required surgical intervention, or experienced complications from adjunctive ICV therapy. In this case series, administration of adjunctive ICV therapy appeared to be a safe, practical, and effective adjunctive therapy for severe *C. difficile* colitis.

With widespread use of broad-spectrum antibiotics and the increasing number of immunocompromised patients, the incidence of *Clostridium difficile* infection has increased dramatically during the past 2 decades [1–4]. In nonepidemic periods, the incidence of *C. difficile* colitis is estimated to be 0.1–30 cases per 1000 patients in nosocomial settings and 8–12 cases per 100,000 person-years in community settings [5–13]. *C. difficile* is associated with 96%–100% of cases of pseudomembranous colitis, 60%–75% of cases of antibiotic-associated colitis, and 11%–33% of cases of diarrhea associated with antibiotic therapy [14–29].

Currently, treatment with orally administered metronidazole and vancomycin is regarded as the standard therapeutic option for *C. difficile* colitis. Bacitracin, teicoplanin, fusidic acid, and colestipol have also been used as alternative agents to treat *C. difficile* colitis [2, 15]. In certain cases, severe disease has led to toxic megacolon, ileus, or toxic enterocolitis, and treatment with standard, orally or intravenously administered regimens of antimicrobials has been unsuccessful because of inadequate intracolonic drug concentrations [30–32]. There are anecdotal reports that treatment of *C. difficile* colitis with adjunctive intracolonic vancomycin (ICV) therapy, which uses an alternative route of administration, has been successful for 57%–75% of patients [8, 33–42]. In this case series, we report the clinical course and treatment outcomes for 9 consecutively hospitalized patients who received ICV as adjunctive therapy for severe *C. difficile* colitis.

METHODS

Case definition. A case patient was defined as a patient who received adjunctive ICV therapy for *C. difficile* colitis at Barnes-Jewish Hospital (St. Louis), a 1442-bed tertiary-care teaching hospital, during the period from 1 January 1998 through 30 June 2001. Patients

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were identified by querying the database of the hospital pharmacy system. Medical records were reviewed to ascertain that these patients had the diagnosis of *C. difficile* colitis and received ICV as adjunctive therapy. A diagnosis of *C. difficile* colitis was made on the basis of a stool specimen positive for *C. difficile* toxin by cytotoxicity assay (Bartels) and ⩾1 of the following findings: clinical symptoms (abdominal pain and/or distension, fever, and/or diarrhea); leukocytosis; radiographic evidence of colitis by CT scan of the abdomen and pelvis; and/or the presence of pseudomembranes, as ascertained either by flexible sigmoidoscopy or by colonoscopy. The decision to initiate adjunctive ICV therapy was made by the individual attending physician. On the basis of a retrospective chart review, all patients met ⩾1 of the following criteria: no clinical response to standard therapy for *C. difficile* colitis (after 5–7 days), severe ileus resulting in cessation of diarrhea and impaired oral intake during the hospital stay, or clinical evidence of fulminant colitis.

Study design. A standardized data-gathering instrument was completed for each case patient. Data collected included demographic characteristics; risk factors for *C. difficile* infection (previous *C. difficile* infection and receipt of treatment for that infection and receipt of antibiotics, chemotherapeutic agents, or other immunosuppressive medications within the previous 6 weeks); past medical history (history of malignancy, leukemia, history of transplantation, and history of *C. difficile*–associated diarrhea [CDAD] or colitis); history of surgery; and clinical presentations such as diarrhea (defined as ⩾3 loose or watery stools per 24 h), fever, and abdominal pain and/or distension. Hypotension at clinical presentation was defined as systolic blood pressure of <80 mm Hg. Information collected by abdominal radiography and abdominal CT scan included the presence and severity of ileus, the severity and site of colitis, and the presence of ascites and pneumatosis. Data on severity of illness included the following: APACHE II score on the day that a stool specimen was submitted for *C. difficile* cytotoxin testing, signs and symptoms of severe illness (fever, chills, dehydration, leukocytosis, and impaired mental status), and enteric colonization with vancomycin-resistant enterococci (VRE). The descriptive outcomes were as follows: survival; presence of concurrent bacteremia during or after treatment; acquisition of enteric VRE after treatment; treatment complications, such as bowel perforation and the need for surgery; and readmission to the hospital for recurrent *C. difficile* infection during the 6-week interval after the completion of treatment for *C. difficile* colitis.

Treatment description and definition of resolution. All patients received adjunctive ICV therapy by enema. Because this was a descriptive study, there were variations in clinical care received, microbiological studies and radiographic evaluations done, the dosages of adjunctive ICV therapy, and the duration of follow-up. For adjunctive ICV therapy, an intravenous solution of vancomycin (0.5–1 g dissolved in 1–2 L of normal saline) was prepared and dispensed by the hospital pharmacy; dosing intervals were defined as every 4–12 h, at the attending physician's discretion. The method of administration recommended by the hospital pharmacy was retention enema. An 18-French Foley catheter with a 30-mL balloon was inserted into the rectum, the balloon inflated, the ICV solution instilled, and the catheter clamped for 60 min. The balloon was then deflated and the catheter removed. The adjunctive ICV therapy was continued until clinical improvement was achieved.

Resolution was defined as clinical improvement after the completion of adjunctive ICV treatment with or without eradication of *C. difficile* cytotoxin production. Complete clinical resolution was defined as discharge from the hospital with no clinical, laboratory, or radiographic findings consistent with ongoing *C. difficile* infection. Partial resolution was defined as some decrease in leukocytosis and no signs of ileus, as assessed by radiography or CT, but continued abdominal distention. Clinical nonresponse was defined as no improvement, minimal improvement, or persistent pancolitis on autopsy.

CASE REPORTS

From the 9 patients who received adjunctive ICV therapy, we selected 3 patients to represent our case series population; we discuss these 3 patients below. The demographic characteristics, comorbidities, and clinical presentations of all patients are listed in table 1.

Patient 1. A 65-year-old woman was transferred to our hospital with fever, abdominal pain, and diarrhea. She was receiving ampicillin-sulbactam for presumed community-acquired pneumonia. One month before, she had undergone right-side colectomy for stage I colon cancer, followed by 2 cycles of fluorouracil therapy. Evaluation revealed fever, abdominal pain and distension, and increased colostomy output. At admission, a stool test was positive for *C. difficile* cytotoxin, and intravenous therapy with ampicillin, gentamicin, and metronidazole was started empirically. Abdominal CT revealed diffuse pancolitis and severe ileus. Because of persistent symptoms, flexible sigmoidoscopy was performed, which revealed diffuse pseudomembranes. Ampicillin and gentamicin were discontinued, and adjunctive ICV therapy was initiated on hospital day 5 (table 2). Five days later, the patient experienced full clinical resolution and eradication of *C. difficile* cytotoxin production. Adjunctive ICV therapy was continued for a total of 7 days. A 4-week course of vancomycin (125 mg po q6h) was prescribed at the time of discharge. At follow-up, 6 weeks after the completion of *C. difficile* colitis treatment, the patient had no recurrent disease, and abdominal CT revealed resolution of the pancolitis.

Patient 2. A 67-year-old woman was transferred to our

Table 1. Demographic characteristics, underlying disease, and clinical presentation of 9 patients with *Clostridium difficile* colitis who received adjunctive intracolonic vancomycin therapy.

Patient [reference]	Sex, age, in years	Medical history[a]	Surgical history[a]	Malignancy[b]	Medication[a]	Presentation[c]	WBCs/μL[c]	APACHE II score[c]
1	F, 65	—	Right colectomy	Colon cancer	ES-Pen, Amp, Mtz, 5-FU	D, AD, F	24,000	15
2	F, 67	COPD, pneumonia, CDAD	—	—	ES-Pen, S	D, AD, AP, H	28,800	20
3	F, 42	—	—	NHL	Ceph, Ara-C, Eps, BCNU, Mel	D, AD, H	8000	17
4	M, 57	COPD	Tongue surgery	Tongue cancer	Cm	D, AD, AP, H	42,000	17
5	F, 81	CDAD	—	—	Mtz	D, AD, AP, F	15,400	12
6	M, 79	CDAD, CRI	—	—	ES-Pen	D, AD, AP, H	73,200	26
7	M, 80	CDAD	Transverse colectomy	Colon cancer	Ceph	D, AD, F	8600	12
8	F, 60	COPD, CHF	Cystocele repair	—	Ceph	D, AD, AP, F, H	33,800	24
9 [42]	F, 32	—	—	AML	Mac	D, AD, AP, F, H	22,700	17

NOTE. 5-FU, fluorouracil; AD, abdominal distension; AML, acute myeloblastic leukemia; Amp, ampicillin; AP, abdominal pain; Ara-C, cytarabine; BCNU, carmustine; CDAD, *Clostridium difficile*–associated diarrhea; Ceph, cephalosporin; CHF, congestive heart failure; Cm, clindamycin; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; D, diarrhea; Eps, etoposide; ES-Pen, extended-spectrum penicillin; F, fever; H, hypotension; Mac, macrolide; Mel, melphalan; Mtz, metronidazole; NHL, non-Hodgkin lymphoma; S, steroid.

[a] Within the previous 6 weeks.

[b] Current active malignancy.

[c] On the day that *C. difficile* cytotoxin was submitted.

hospital with severe abdominal pain, diarrhea, and severe ileus and diffuse colitis (as revealed by abdominal CT). Her medical history was remarkable for corticosteroid-dependent chronic obstructive pulmonary disease and pneumonia that had been diagnosed 2 weeks before admission to our hospital and had been treated with piperacillin-tazobactam. At admission, she had fever, severe abdominal pain and distension, and diarrhea. The result of a stool test for *C. difficile* cytotoxin was positive. To treat presumed clinical sepsis, aggressive hydration was initiated as well as antimicrobial therapy with intravenous cefepime and metronidazole, oral vancomycin (via nasogastric tube), and adjunctive ICV (table 2). The patient declined surgical intervention. The hospital course was complicated by sepsis of unknown etiology and progressive multisystem organ failure. All medical support was withdrawn at the request of the patient's family, and the patient died on hospital day 10. An autopsy was declined by the patient's family. No evidence of clinical efficacy was observed after the initiation of adjunctive ICV therapy.

Patient 3. A 42-year-old woman with a history of recurrent non-Hodgkin lymphoma underwent elective autologous stem-cell transplantation on hospital day 8. The hospital course was complicated by neutropenia, fever, diarrhea, and hypotension requiring pressors on hospital day 10. Empiric therapy with cefepime for possible sepsis was begun. At that time, the result of a stool test for *C. difficile* cytotoxin was positive, and therapy with intravenous metronidazole was initiated on hospital day 12. The patient developed abdominal pain and distension, and abdominal CT revealed severe ileus and right-side colonic inflammation. Adjunctive ICV therapy was begun on hospital day 17. Resolution of ileus and full clinical recovery occurred after 5 days of ICV treatment, and this was followed by a 2-week course of oral metronidazole (table 2). Subsequently, the result of a test for *C. difficile* cytotoxin was negative. Notably, the hospital course was complicated by catheter-associated VRE bacteremia, which was treated by catheter removal. There was no recurrence of *C. difficile* colitis during the 6 weeks after the completion of metronidazole therapy.

RESULTS

Patient characteristics, risk factors, and clinical presentation. The median age of patients was 65 years (range, 32–81 years); the majority (6 [66.7%] of 9) were women, and all were white. Seven (77.7%) of the 9 patients were admitted to the hospital for *C. difficile* colitis, and 2 (22.2%) developed *C. difficile* colitis while hospitalized. The medical histories of the patients included hypertension (9 [100%] of patients), chronic obstructive pulmonary disease (3 [33.3%]), renal insufficiency (1 [11.1%]), underlying solid-organ tumor (3 [33.3%]; 2 patients with colon cancer and 1 with tongue cancer), and leukemia (1 patient with non-Hodgkin lymphoma and 1 patient with acute myeloblastic leukemia) for which stem-cell transplantation had been done during the previous 3 months (2 [22.2%]). All patients had a history of antibiotic use, and 2 patients (22.2%) had received chemotherapy within 6 weeks of presentation. One patient (11.1%) was receiving concurrent corticosteroid treatment. In addition, 2 patients (22.2%) had history of gastrointestinal surgery, and 2 (22.2%) had history of other surgical procedures (tongue surgery and cystocele repair). Four patients (44.4%) had a history of CDAD within the 6 weeks before admission.

Table 2. Diagnosis, treatment, and outcome for 9 patients with *Clostridium difficile* colitis who received adjunctive intracolonic vancomycin (ICV) therapy.

Patient [reference]	Radiography finding[a]	Sigmoidoscopy finding	ICV dosage (duration, days)	Concurrent anti–*C. difficile* medication	Surgery consultation (surgery)	Clinical resolution (outcome)	Eradication of cytotoxin production after ICV therapy	Bacteremia or fungemia (etiologic agent)[b]
1	Diffuse colitis	PMC	1 g q12h (7)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	Complete (recovered)	Yes	No
2	Diffuse colitis	ND	1 g q12h (10)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	No (died)	ND	No
3	Right-side colitis	ND	0.5 g q4h (5)	Mtz (iv), Mtz (po)	Yes (No)	Complete (recovered)	Yes	Yes (VRE)
4	Diffuse colitis	ND	0.5 g q4h (4)	Mtz (iv), Mtz (po), Vm (po)	No	Complete (recovered)	ND	No
5	Left-side colitis	PMC	1 g q12h (4)	Mtz (iv), Mtz (po)	No	Complete (recovered)	ND	No
6	Left-side colitis	PMC	0.5 g q8h (14)	Mtz (iv), Mtz (po), Vm (po), Lact, Bct	Yes (No)	Complete (recovered)	Yes	Yes (VRE)
7	Diffuse colitis	ND	1 g q8h (2)	Mtz (iv), Mtz (po), Vm (po)	No	Complete (recovered)	ND	No
8	Diffuse colitis	ND	0.5 g q6h (9)	Mtz (iv), Mtz (po), Vm (po), Lact, Bct	No	Complete (recovered)	No	Yes *(Citrobacter freundii)*
9 [42]	Diffuse colitis	Diffuse edema	0.5 g q6h (6)	Mtz (iv), Mtz (po), Vm (po)	Yes (No)	Complete (recovered)	ND	Yes (*Candida glabrata*, CNS)

NOTE. All patients had confirmed *C. difficile* toxin by cytotoxicity assay (Bartels' Cytotoxicity Assay; Bartels). Bct, bacitracin; CNS, coagulase-negative staphylococci; Lact, lactobacillus; Mtz, metronidazole; ND, not done; PMC, pseudomembranous colitis; Vm, vancomycin; VRE, vancomycin-resistant enterococci.

[a] Abdominal CT scan, plain abdominal film at the onset of symptoms, or both.

[b] Bacteremia or fungemia after the initiation of ICV therapy.

Although all 9 patients presented with diarrhea and abdominal distension, 6 (66.7%) presented with abdominal pain, and 5 (55.6%) were febrile at admission. ICV was administered as an adjunctive regimen to patients whose illness failed to improve after 5–7 days of standard therapy for *C. difficile* colitis (8 [88.9%] of 9 patients), to those with evidence of severe ileus resulting in cessation of diarrhea and impaired oral intake (8 [88.9%] of 9), and to those with clinical evidence of fulminant colitis (2 [22.2%] of 9). The median APACHE II score was 17 (range, 12–26), and hypotension was noted in 6 patients (66.7%) at the time of diagnosis of *C. difficile* colitis.

Laboratory and radiography results. The median leukocyte count was 24,000 cells/μL (range, 8000–73,200 cells/μL). Two patients (22.2%) had leukocyte counts within the normal range throughout their clinical illness. All 9 patients had stool specimens positive for *C. difficile* by cytotoxicity assay, and 4 (44.4%) had test results positive for enteric VRE before the initiation of adjunctive ICV treatment. Abdominal radiographs were obtained for 8 (88.9%) of 9 patients, and abdominal CT scans were performed for 7 patients (77.8%). Colitis was observed in the left colon of 2 patients (22.2%) and in the right colon of 1 patient (11.1%), and diffuse colitis was observed in 6 patients (66.7%). Severe ileus was noted in 8 patients (88.9%), ascites in 2 patients (22.2%), and pneumatosis in 1 patient (11.1%). Sigmoidoscopy was performed for 4 (44.4%) of the 9 patients and revealed evidence of pseudomembranes in 3 (75%) of those 4.

Treatment and outcomes. All patients received adjunctive ICV therapy by rectal enema. Adjunctive ICV therapy was continued until clinical improvement was achieved. Although complete clinical resolution was achieved in 8 patients (88.9%), *C. difficile* cytotoxin production eradication was documented in 3 (75%) of 4 patients who were tested again after the completion of treatment. The duration of adjunctive ICV therapy ranged from 2 to 14 days (table 2). No patient acquired enteric VRE after adjunctive ICV treatment. Bacteremia developed in 4 patients (44.4%), one of whom also developed fungemia with *Candida glabrata.* The organisms isolated were VRE (2 patients), *Citrobacter freundii* (1), coagulase-negative *Staphylococcus* species (1), and *C. glabrata* (1). VRE bacteremia occurred in 2 (50%) of 4 patients who had prior enteric colonization with VRE. No patient underwent surgery for complications related to *C. difficile* infection or developed recognized complications of adjunctive ICV therapy. Six patients (66.7%) were discharged home, 2 patients (22.2%) were transferred to rehabilitation facilities, and 1 patient (11.1%) died as a result of progressive multisystem organ failure. No patient experienced a subsequent episode of *C. difficile* colitis or CDAD, and no patient developed treatment complications during the 6 weeks after the completion of treatment for *C. difficile* colitis.

DISCUSSION

This small case series complements a short list of published observational data supporting the use of adjunctive ICV therapy for selected patients with *C. difficile* colitis. Adjunctive ICV therapy appeared to be safe, practical, and effective for treatment of severe *C. difficile* colitis. It seemed effective for both first and recurrent episodes of *C. difficile* colitis in patients for whom standard therapy had failed, who had severe ileus resulting in impaired oral intake while hospitalized.

Overall, an estimated 5% of healthy asymptomatic adults are enteric carriers of *C. difficile* [43]. When associated with disease, the presence of *C. difficile* cytotoxin can result in severe conditions, including perforation of the colon, prolonged ileus, toxic megacolon, and death [1, 44–45]. Although infrequent, surgical intervention is considered a treatment option for patients with organ failure, worsening radiographic evidence of colitis, and peritonitis [1, 44–46]. Apart from surgical intervention, an alternative therapy for critically ill patients who are unable to take oral antimicrobial agents is intravenous metronidazole [1, 44–45, 47]. In these circumstances, intravenous metronidazole therapy produces fecal concentrations greater than the MIC for *C. difficile* and may be an effective therapy [47]. Nevertheless, the efficacy of intravenous metronidazole therapy remains questionable. Metronidazole excretion occurs mainly in the upper part of the gastrointestinal tract; ~14% of each dose of intravenously administered metronidazole is excreted in the feces [40]. Although some data suggest that antibiotic-associated colitis can be successfully treated with intravenous metronidazole [47, 48], other data report therapeutic failure in the presence of adynamic ileus [49]. In addition, the delivery of metronidazole was unpredictable in patients with ileus or toxic megacolon [8], and the amount of the drug and its metabolite detected declined over time as clinical resolution occurred [47]. Therefore, adjunctive ICV treatment administered by rectal enema or through long catheters is an alternative regimen for severely ill patients who either are not eligible for or do not respond to first-line therapeutic regimens [8, 33–42].

George and colleagues [21] first recommended the use of adjunctive ICV therapy in patients with ileus or toxic megacolon. Griebie and Adams [33] reported success with adjunctive ICV therapy for *C. difficile* colitis for a patient who had undergone head and neck surgery and had severe ileus and colonic obstruction. Several case reports have claimed that adjunctive ICV therapy was effective for treatment of *C. difficile* colitis in patients with severe ileus or impaired oral intake [8, 34–42]. Olson and colleagues [8] reported the successful use of a standard initial dose of adjunctive ICV therapy for 6 (75%) of 8 patients who had *C. difficile*–associated disease and severe ileus. Shetler and colleagues [40] subsequently suggested that colonoscopic decompression combined with adjunctive ICV therapy could be used to treat severe pseudomembranous colitis as-

sociated with ileus and toxic megacolon. This approach was safe, feasible, and effective; it resulted in complete clinical resolution for 4 (57%) of 7 patients and partial clinical resolution for 1 patient (14%) [40]. Together, these reports suggest that adequate concentrations of ICV can be delivered to the site of *C. difficile* toxin production and inhibit it.

Several recommendations exist for adjunctive ICV treatment of *C. difficile* colitis [21, 30, 43, 50–53]. In our observational study, we identified a variety of dosing intervals and treatment durations used for adjunctive ICV therapy for *C. difficile* colitis. Similar to Olson et al. [8], we found a wide range in the time to clinical response (range, 2–14 days). Our observations suggest that surgical intervention was rarely indicated for *C. difficile* colitis after adjunctive ICV therapy was initiated, a finding noted by others [8, 40]. We also noted an association between the resolution of leukocytosis and a favorable clinical response [40].

Oral administration of vancomycin can lead to significant serum levels in the presence of either intense mucosal inflammation or decreased elimination of the drug as a result of renal failure [54, 55]. To avoid neurotoxicity and nephrotoxicity, the adjunctive ICV therapy dosage should be reduced to maintain a serum concentration of <30–40 mg/L in patients with renal insufficiency [54, 55]. Thus, after administration of ICV to such patients, monitoring of vancomycin levels in serum should be considered, in order to enhance the safety of this treatment [54, 56].

There are theoretical and practical concerns regarding the potential efficacy of delivery of ICV to the transverse and right colon. In our literature review, we identified successful outcomes in 20 (83.3%) of 24 episodes of *C. difficile* colitis treated with adjunctive ICV therapy [8, 33–42]. It is possible that inadequate delivery of ICV to the proximal colon contributed to treatment failure in some patients. In our case series, the initial adjunctive ICV therapy dosage was 2–3 g/day with dosing intervals of 4–12 h. Although this was safe and effective in the majority of patients, other investigators have recommended use of standard initial doses and dosing intervals [8, 40, 50].

Our study was limited by its retrospective design and inherent variations in the radiologic data, dosage, and duration of adjunctive ICV therapy and in the confirmation of eradication of cytotoxin production for each patient. Although bacteremia and fungemia occurred in 4 patients, the attributable risk associated with adjunctive ICV therapy was unable to be determined from these observational data. Because these were retrospective data, we were unable to identify any issues regarding the efficacy, safety, and toxicity of adjunctive ICV therapy that may have been considered by the prescribing physicians.

Given the high clinical response rate and favorable outcomes for this case series, ICV may be considered as an adjunct to the standard regimen of antimicrobial therapy for severe *C. difficile* colitis in selected patients. However, the issues of the efficacy, dosage, and duration of adjunctive ICV therapy remain to be addressed in future studies.

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