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ORIGINAL RESEARCH

Intravenous Immunoglobulin for the Treatment of Severe *Clostridium difficile* Colitis: An Observational Study and Review of the Literature

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BACKGROUND: *Clostridium difficile* colitis (CDC) is the most common cause of hospital-acquired diarrhea. The increase in the incidence and fatality rate of CDC over the past decade has stimulated a search for new therapies, including intravenous immunoglobulin (IVIG). We report our experience with IVIG for the treatment of 21 patients with severe CDC.
METHOD: Retrospective review of patients with severe CDC who received IVIG between July 2002 and April 2006 at a teaching hospital. The existing literature on IVIG infusion for severe CDC was also reviewed.
RESULTS: Twenty-one of 1230 patients with CDC were treated with IVIG. The mean age was 68 (range, 35–98) years, with mean hospital stay of 23 (range, 9–64) days. Conventional treatment was used for an average of 8 (range, 1–25) days before IVIG infusion. All patients had evidence of pancolitis (radiologically) or ileus (clinically). The mean Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score was 25 (range, 6–39) at day 1 of IVIG infusion. Nine patients (43%) survived their hospitalization with colitis resolution while 12 (57%) died. One patient developed pulmonary edema after IVIG infusion. Symptoms resolved after an average of 10 (range, 2–20) days for survivors. Two patients underwent urgent colectomy.
CONCLUSIONS: This is the largest case series describing IVIG use for patients with severe CDC and the one with the highest mortality rate to date. The use of IVIG in this setting does not seem to benefit all patients. Benefit appears to depend on the extent of systemic involvement. Further studies are needed before adopting IVIG as routine treatment for severe CDC.
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KEYWORDS: **clostridium difficile, diarrhea, immunity, immunoglobulin, nosocomial infection.**

Clostridium difficile colitis (CDC) is the most common cause of hospital-acquired diarrhea.[1] The incidence of CDC has sharply increased over the past decade despite increasing awareness among health care professionals.[2–4] *C. difficile* pathogenic strains induce diarrhea through the elaboration and secretion of 2 exotoxins: toxin A and toxin B. Toxin A is an inflammatory toxin, leading to fluid secretion, increased mucosal permeability, and marked enteritis and colitis.[5] Toxin B is cytotoxic, leading to cell injury and apoptosis.[5] Combined, toxin A and toxin B can cause a wide spectrum of clinical presentations, ranging from mild diarrhea that resolves with the discontinuation of antibiotics to a fulminant colitis requiring surgical intervention.

The severity of clinical manifestations has been shown to be inversely proportional to the host anti-toxin A antibody level in response to toxin exposure. Kyne et al.[6] demonstrated that asymptomatic *C. difficile* carriers produced significantly higher anti-toxin A immunoglobulin G (IgG) levels compared to symptomatic patients. Among the latter group, patients with mild disease had a higher antibody level compared to those with severe colitis.[6,7] Additional risk factors predisposing to severe colitis are advanced age, severe underlying illness,[8] and immunocompromised state.[9]

Recently, a new *C. difficile* strain (BI/NAP1) with a mutated toxin A and toxin B promoter silencer, a binary toxin gene, and fluoroquinolone resistance has been described in Canada and the United States.[3,10] This strain has been associated with an increased incidence of CDC among hospitalized patients, especially the incidence of severe disease requiring colectomy. At the same time, several reports describing metronidazole treatment failure have been published.[11–14] These recent findings emphasize the importance of finding alternative treatments for CDC.

Intravenous immunoglobulin (IVIG) was used to treat CDC for the first time in 1991.[15] Since then, 12 case reports and small case series, along with 1 case-control study have been published documenting IVIG treatment outcomes.[15–27] However, only 5 reports to date examined patients with

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severe CDC.[21–25] In the present study, we report the largest series of patients with severe CDC treated with IVIG in the literature to our knowledge.

Patients and Methods

Case Series

We used CareScience software (CareScience, Inc., Philadelphia, PA) to retrospectively identify all patients admitted to our institution with a primary or secondary diagnosis of CDC (code 00845) between July 1, 2002 and May 1, 2006. CareScience is commercially available software that tracks all admissions to our institution and allows the performance of patient searches with a wide spectrum of user-defined search criteria. Using the same software, we further identified those patients who received IVIG during their hospital stay. We then obtained the hospital chart for each patient, from the medical records department and established the study database.

A case was defined as a patient with diarrhea (at least 3 loose stools daily) for at least 2 days who had *C. difficile* cytotoxin-positive feces and at least 1 of the following criteria: clinical symptoms (abdominal pain and/or distension and fever); leukemoid reaction (defined as white blood cell count of 20,000 cells/mm^3 or above. This cutoff value was chosen as it has been used previously as a prognostic factor)[4]; radiographic evidence of colitis by computed tomography (CT) of the abdomen; and/or the presence of pseudomembranes on flexible sigmoidoscopy or colonoscopy. We excluded all patients who received IVIG for an indication other than CDC treatment (n = 3). There were no other exclusion criteria.

We used a standardized data collection tool and recorded demographics (age, gender, principal diagnosis), past medical and surgical history, other risk factors for *C. difficile* infection (previous CDC, antibiotics received during hospital stay, immunosuppressive medications or organ transplantation within the previous 6 weeks, history of malignancy or diabetes mellitus); clinical presentation (abdominal distention, abdominal pain, diarrhea, fever, leukemoid reaction, and hypotension defined as systolic blood pressure <85 mm Hg despite at least 1 L of intravenous normal saline administration and the need for vasopressor use); colonoscopy findings; CT scan and x-ray findings; laboratory values; date and dose of IVIG infused and other *C. difficile* pharmacological treatments; and Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score[28] at the first day of IVIG infusion. The primary outcomes were survival at the end of the hospital stay and clinical disease resolution, defined as 2 formed bowel movements or less per day without abdominal pain or distention.

The decision to initiate IVIG therapy and the dose to be used was made by the individual attending physician.

Statistical Analysis

Single (univariate) and multiple (multivariate) logistic regression analysis were applied to identify variables among the ones collected that are independent predictors of CDC mortality. All statistical analyses were completed with the STATA 10 software package (StatCorp LP, College Station, TX).

Review of the Literature

We used PubMed, Web of Science, Scopus, and Excerpta Medica databases to search for any publication in a peer-reviewed journal on the use of IVIG for the treatment of severe CDC. We used the search words: "IVIG" or "intravenous immunoglobulin" and "clostridium difficile." Only publications published in English were selected. The date range used was January 1, 1950 to January 7, 2009. We were able to find 5 publications using this search criteria.

Results

Study Population

Of the 1230 patients diagnosed with CDC over the 4-year study period, 21 patients were treated with IVIG. Table 1 summarizes the patients' characteristics. There were 13 women and 8 men. The mean age was 68 years, with a standard deviation (SD) of 13 years. Sepsis was the primary diagnosis in all patients. Sixteen patients had predisposing risk factors for CDC, including immunosuppression (immunosuppressive medication [n = 2], human immunodeficiency virus [HIV] infection [n = 2]); cancer (n = 3); recent surgery (n = 3); and diabetes mellitus (n = 11). Nine patients had documented previous CDC episodes. The indications for IVIG administration were evidence of pancolitis on abdominal CT scan (n = 12) or severe ileus with cessation of diarrhea, abdominal distention, and requirement for total parenteral nutrition (n = 5), or severe hypotension (n = 4) (defined as systolic blood pressure <85 mm Hg despite at least 1 L of intravenous normal saline administration and the subsequent need for vasopressor use).

Table 2 describes disease severity in these patients. Since CDC starts locally in the colon then secondarily involves multiple organs as part of the systemic inflammatory response syndrome (SIRS), 2 scales were used to characterize the disease in each patient: (1) extent of local colonic inflammation, and (2) severity of systemic involvement. Extensive colonic involvement was evidenced in all patients by pancolitis on abdominal imaging modalities (12 patients), severe ileus requiring total parenteral nutrition (13 patients), or referral for surgical consultation for possible colectomy (12 patients).

Of the 21 patients treated with IVIG, 9 did not receive a surgical consultation either because they responded to medical treatment promptly (6 patients), were too unstable for surgery (2 patients), or because the patient/family refused surgery (1 patient). Of the 12 patients who received surgical consultation, 2 underwent surgery. The remainder did not proceed to surgery for the following reasons: they were deemed medically unstable for surgery (6 patients), declined surgery (2 patients), were diagnosed with cancer on colonoscopy (1 patient), or improved with medical treatment (1 patient).

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TABLE 1. Patients' Characteristics and Presentation

Patient	Age (gender)	Diagnosis	Medical and Surgical History	CDC History	Colonoscopy Findings	Radiographic Findings
A	40 (female)	CDC with sec. sepsis	Gastric stapling	Yes	*	Diffuse colitis†
B	86 (female)	Fulminant CDC	Metastatic ovarian carcinoma		PC	No colonic thickening†
C	72 (male)	Sepsis	Acute pancreatitis with sec. pseudocyst, DM	Yes	PC	Diffuse colitis†
D	78 (male)	Discitis			Delayed: normal mucosa	Dilation of small and large bowel†
E	98 (female)	Urosepsis		Yes	*	No bowel distention‡
F	90 (female)	Right lower extremity cellulitis	DM		*	Concentric thickening of rectal wall†
G	64 (male)	Ischemic colitis	DM, recent Hartman pouch closure		Marked inflammation	Diffuse colitis†
H	78 (female)	Toe osteomyelitis and CDC with sec. sepsis	DM		*	Diffuse colitis†
I	35 (female)	Sepsis		Yes	*	Diffuse nonspecific colitis, minimal ascites†
J	47 (female)	Pneumonia and sec. sepsis			*	Diffuse colitis†
K	56 (female)	Urosepsis	HIV	Yes	*	Colitis involving the right colon†
L	76 (male)	CDC with sec. sepsis	Sigmoid bladder fistula repair, DM		*	Diffuse colitis†
M	71 (female)	Pneumonia with sec. sepsis			*	Diffuse colitis†
N	63 (male)	Urosepsis	DM, lymphoma resection from small intestine		PC	Marked small and large bowel distention‡
O	86 (male)	Enterococcus-induced sepsis	Rheumatoid arthritis on methotrexate		*	Fat stranding suggesting peritonitis†
P	60 (female)	Gastrointestinal bleed and CDC	DM with neuropathy and retinopathies	Yes	*	Thickening of wall of colon in most of the colon‡
Q	57 (female)	Sepsis	DM	Yes	*	Normal‡
R	67 (female)	CDC with sec. sepsis	Candidal esophagitis	Yes	*	Large amount of peritoneal fluid, mild small bowel thickening‡
S	60 (female)	Sepsis sec. to *S. aureus* and *P. aerogenosa*	DM, renal transplant (myco, prednisone)		*	Ileus with air fluid level in the small intestine‡
T	80 (female)	Sepsis	DM	Yes	*	Thickening of descending colon consistent with colitis‡
U	72 (male)	CDC, widespread metastatic cancer	DM, metastatic cancer (unknown primary site)		*	Severe colitis up to the splenic flexure†

Abbreviations: AD, abdominal distension; AP, abdominal pain; CAT, computerized axial tomography; CDC, *Clostridium difficile* colitis; D, diarrhea; DM, diabetes mellitus; F, fever; HT, hypotension; L, lymphocytosis; myco, mycophenolate mofetil; PC, pseudomembranous colitis; sec, secondary.

*Colonoscopy not performed.

†Finding on CAT scan of abdomen and pelvis.

‡Finding on abdominal X-ray.

The severity of systemic involvement was measured using the APACHE II score on day 1 of IVIG infusion. The mean APACHE II score was 25. Eighteen patients were in a monitored unit when IVIG was administered. The study group had laboratory results in keeping with those previously used to define severe colitis:[4,9,19] leukocytosis (defined as white blood cell count higher than 12,000 cells/mL [mean = 36,000 cells/mL]), hypoalbuminemia (mean = 1.78 g/dL, SD = 0.68 g/dL), hypokalemia (mean = 3.02 mg/dL, SD = 0.47 g/dL), and acute renal failure (defined as serum creatinine level >1.5 mg/dL [mean = 2.98 mg/dL, SD = 1.42 g/dL]).

IVIG Use

Table 3 describes the treatment patients received for CDC as well as the total number of antibiotics used throughout the hospital stay. IVIG was used as adjuvant treatment (defined as IVIG administration within 4 days or less after CDC diagnosis) in 8 patients and as second-line treatment (defined as IVIG administration more than 4 days after CDC diagnosis) in 13 patients. Metronidazole, vancomycin, cholestyramine, and probiotic treatment alone or in different combinations were used for an average of 8 days (SD = 8 days; range, 0–25 days) before IVIG infusion. The total IVIG dose administered varied depending on the prescribing attending, with a range of 200 mg/kg to 1250 mg/kg and a mode of 250 mg/kg for 1 to 3 days. An average of 5 (SD = 2) different antibiotics that were not active against *C. difficile* were used per patient without being discontinued after a CDC diagnosis was made. The 3 most common were: cephalosporins (cefazolin, ceftriaxone, cefepime), fluoroquinolones (levofloxacin), and combination antibiotics (piperacillin and tazobactam or ampicillin and sulbactam).

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TABLE 2. Disease Severity

Patient	Complications During the Hospital Stay	APACHE II Score	Monitored Unit	WBC*	K†	Alb†	Lactate‡	Cr†	Hospital Stay (days)	Surgical Consult/ Surgery	TPN for Colitis
A	Sepsis, DIC, ARDS, intubation	15	Yes	48	4	1.1	2.9	1.3	26	No/No	Yes
B	Dehydration, weakness	12	No	19	3.4	3.1	—	1.1	16	No/No	Yes
C	HTP, GI bleed, ischemic colitis, F	22	Yes	21	2.7	2.5	1.3	ESRD	34	Yes/No	Yes
D	AD, megacolon, HT, intubation, ARF	18	Yes	25	3.4	1.4	1.1	2.6	52	Yes/No	Yes
E	Exacerbation of CHF with respiratory distress, Bipap support, confusion	21	No	10	2.6	2.3	—	1	11	No/No	No
F	Confusion, gout acute attack	21	No	33	3.1	2.6	—	ESRD	15	No/No	No
G	Intubation, cardiac arrest, AF with RVR, PNA, ARF, DVT, dysphagia, PEG	6	Yes	15	3.1	1.7	1.9	2.2	32	Yes/No	Yes
H	Sepsis, intubation, ARF, PEG, toe amputation, PNA, pulmonary edema, TPN, vitamin D deficiency	34	Yes	59	2.8	1.5	4	3.8	17	No/No	Yes
I	CHF, transient third cranial nerve palsy, DIC	20	Yes	52	3.2	3.3	0.7	ESRD	11	No/No	No
J	Aspiration PNA, sepsis, DIC, intubation, MI, F, HT	32	Yes	17	2.7	1.8	14	ESRD	21	Yes/no	No
K	Intubation, cardiac arrest, ARF, DIC, AP, F	30	Yes	25	2.1	2.1	13	3.6	10	Yes/no	No
L	Intubation, ARF, HTP, MI, AD, F	23	Yes	69	3.2	1.8	1.4	3.6	23	Yes/no	No
M	Intubation, DIC, ARF, GI bleeding, hypothermia, AD	23	Yes	47	2.8	1.4	1.4	4.3	23	Yes/no	Yes
N	Intubation, HTP, AD, F, ARF with HD, AF, osteomyelitis	23	Yes	46	2.9	1.5	1.5	2.7	27	Yes/no	Yes
O	Intubation, ARF, 2 cardiac arrests, GI bleed, UTI, rhabdomyolysis, liver shock, AF	31	Yes	49	2.5	1.1	2.3	2.9	25	Yes/no	Yes
P	Bowel ischemia with bowel resection, ARF, MI, ischemic bowel, fluid overload, respiratory failure	23	Yes	26	2.6	0.8	2.9	3.1	9	Yes/Yes	Yes
Q	Pulmonary embolism	39	Yes	23	2.8	1.1	8.1	ESRD	9	No/No	Yes
R	Fungal peritonitis, aspiration pneumonia, cardiac arrest	26	Yes	30	4.1	1.1	0.9	ESRD	36	No/No	Yes
S	Intubation, pneumothorax, CRT, pressor-dependent shock, ARF	36	Yes	46	3.1	1.8	2.1	5.4	64	Yes/Yes	No
T	Pressor-dependent sepsis, pulmonary edema, ARF with HD	36	Yes	35	3.3	1.3	1.8	5.5	11	Yes/No	Yes
U	Sepsis	34	Yes	58	3.1	2.2	3.3	1.6	9	No/No	No

NOTE: Lactate level elevation is more difficult to interpret in patients with ESRD since the elevation is a combination of production and delayed excretion.

*Highest number during hospitalization. Unit is cells/cm^3.

†Lowest number during hospitalization. Units are as follows: K, mg/dL; Alb, g/dL; and Cr, mg/dL.

‡Measured on first day of IVIG infusion. When not available on the same day, last known level before IVIG infusion was reported. Units used: mmol/L.

Abbreviations: AD, abdominal distension; AF, atrial fibrillation; Alb, albumin; ARDS, adult respiratory distress syndrome; ARF, acute renal failure; Bipap, bimodal positive airway pressure; C.Diff., *Clostridium difficile*; Cr, creatinine; DIC, disseminated intravascular coagulopathy; DVT, deep venous thrombosis; ESRD, end-stage renal disease, F, fever; GI, gastrointestinal; HD, hemodialysis; HT, hypotension requiring a pressor agent; IVIG, intravenous immunoglobulin; K, potassium; MI, myocardial infarction; PEG, percutaneous endoscopic gastrostomy tube placement; PNA, pneumonia, RVR, rapid ventricular response; TPN, total parenteral nutrition; UTI, urinary tract infection; WBC, white blood cell count.

Survival with IVIG Use

Nine patients (43%) survived their illness and were discharged from the hospital. They experienced complete clinical resolution after an average of 10 days from IVIG administration (range, 2–20 days) (Table 4). The other 12 patients (57%) died during the index hospitalization. The average length of stay was 23 (range, 9–64) days.

To further assess the impact of IVIG on colitis resolution, we investigated all variables in the data set that may have been associated with mortality using univariate Cox regression analysis. Those variables were as follows: APACHE II score on the first day of IVIG infusion, age, sex, previous history of CDC, number of days before IVIG use, peak white blood cell count, serum potassium level and creatinine level, lactate level on first day of IVIG infusion, and number of antibiotics administered that are not active against CDC. Only the APACHE II score ($P = 0.006$) and lactate level on the day of IVIG infusion ($P = 0.004$) were (positively) associated with CDC mortality. The positive association between CDC mortality and APACHE II score remained significant ($P = 0.04$) after adjusting for sex, previous history of CDC, number of days before IVIG use, lactate level on first day of

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TABLE 3. *Clostridium difficile* Colitis Treatment

Patient	Number of Antibiotics	Duration of Treatment Before IVIG (days)	Treatment Before IVIG (days)	Total CDC Treatment (days)	IgG Level	IVIG Dose
A	5	7	Metro (7), Vanc (7), Choles (2)	Oral and rectal Vanc (26,19), IV Metro (19), Choles (2), Lacto (6)	Low	300 mg/kg for 1 day
B	1	13	Metro (13), Vanc (13)	Oral Vanc (17) and IV Metro (12)		300 mg/kg for 1 day
C	3	7	Metro (7), Vanc (3)	IV Metro (28),Vanc oral and enema (18,3), Lacto (10)	Low	125 mg/kg for 5 days
D	5	25	Metro (25), Vanc (15)	Oral then IV Metro (10,15), oral Vanc (25), Choles (7) and Lacto (13)	Low	200 mg/kg for 1 day
E	1	4	Metro (1), Vanc (4), Choles(4)	IV Metro (8), oral Vanc (10) and Choles (4)		75 mg/kg for 5 days
F	4	2	Metro (2), Vanc (1)	IV Metro (8) and oral Vanc (9)		250 mg/kg for 5 days
G	3	17	Metro (17), Vanc (14)	IV Metro (49) and oral Vanc (61)		250 mg/kg for 2 days
H	5	1	Metro (1), Vanc (1)	Oral Metro (18), oral Vanc (22), IV Metro (3)		250 mg/kg for 3 days
I	6	1	Metro (1)	Oral and IV Metro (7,9), Vanc oral and enema (8,3)		250 mg/kg for 2 days
J	8	16	Metro (14), Vanc (2), Lacto (6)	Oral then IV Metro (10,5), oral and rectal Vanc (3,1), Lacto (6)		300 mg/ kg for 1 day
K	6	7	Metro (7), Vanc (3)	Oral then IV Metro (10) and oral Vanc (9)	Normal	400 mg/kg for 2 days
L	4	0	None	IV then oral Metro (7,10), oral Vanc (23), Choles (7), and Lacto (5)		150 mg/kg for 5 days
M	6	1	Metro (1)	IV Metro (23) and oral Vanc (9)		250 mg/kg for 2 days
N	7	1	Metro (1), Vanc (1)	IV Metro (16), oral Vanc (14), oral Metro (7)		250 mg /kg for 2 days
O	6	7	Metro (6), Vanc (4)	IV Metro (6) and oral Vanc (22)	Low	250 mg/kg for 2 days
P	3	6	Metro (6), Vanc (6)	IV Metro (25) and oral Vanc (17)		150 mg/kg fro 3 days
Q	3	4	Metro (4), Vanc (3)	Oral Metro (8),Vanc oral and enema (6,3)		250 mg/kg for 3 days
R	5	9	Vanc (9)	Vanc oral and enema (5,4), IV Metro (2)		250 mg/kg for 1 day
S	8	23	Metro (23), Vanc (23)	Oral then IV Metro (12,22), oral Vanc (39)		250 mg/kg for 3 days
T	4	6	Metro (6), Vanc (1)	Oral Vanc and IV Metro (11)		250 mg/kg for 1 day
U	4	2	Metro (2), Vanc (2)	Oral Vanc and IV Metro (6)		250 mg/kg for 3 days

Abbreviations: CDC, *Clostridium difficile* colitis; Choles, cholestyramine; IgG, immunoglobulin G; IV, intravenous; IVIG, intravenous immunoglobulin; Lacto, lactobacillus; Metro, metronidazole; Vanc, vancomycin.

IVIG infusion, and number of antibiotics administered that are not active against CDC using a multivariate Cox regression analysis model. No adjustments were made for age, white blood cell count, potassium level, or creatinine level as those are included within the APACHE II score. The positive association between lactate level on the first day of IVIG infusion and CDC mortality was not statistically significant after adjusting for the factors listed above in the same model ($P = 0.13$).

Discussion

To our knowledge, the present study is the largest series published in the literature to date on the use of IVIG for severe CDC. It is also the first study to report a high mortality rate compared to the 5 previous smaller studies on this topic. In the first report on IVIG use for CDC, Leung et al.[15] used IVIG to treat 5 pediatric patients suffering from chronic relapsing CDC. It was not until 7 years later, in 1997, that the first IVIG use for severe CDC was reported.[22] Since then, a total of 13 works have been published on IVIG for CDC treatment, and only in 5 of these was IVIG administered for severe CDC treatment:[21–25] 3 case reports, 1 case series, and 1 case-control study. Although the 4 uncontrolled reports concluded that IVIG is beneficial for severe CDC, the only controlled study reported no significant difference between cases and controls for all-cause mortality, length of stay, and colectomy rate.[25]

The definition of severe CDC varied between reports, making comparison difficult. McPherson et al.[21] and Hassoun and Ibrahim[24] defined severe disease as one causing pancolitis on CT scan either with or without megacolon. In the study by Juang et al.,[25] disease severity was assessed using the modified criteria of Rubin et al.[9] Salcedo et al.[22] defined severe CDC as one causing pancolitis in one patient and thumbprinting on CT scan in another, whereas Chandrasekar et al.[23] defined it as one causing shock requiring inotropic support and presence of pseudomembranes on colonoscopy.

The present report is unique in that it provided 2 scales to characterize disease in each patient. The first scale measured colonic involvement anatomically and physiologically using a combination of computerized axial tomography (CAT) scan findings, presence or absence of ileus or referral for possible colectomy. This is not a prognostic scale, however, since CAT scan findings have been previously shown to be poor predictors of treatment outcome.[29] The second scale measured the severity of systemic involvement using a well-validated and standardized scale, the APACHE II score. We have shown in this report that it is associated with prognosis in the context of IVIG use.

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Our study reports a higher mortality rate than previously described, and suggests that risk stratification and patient selection are important before IVIG administration, since not all patients seem to benefit from this treatment as previously suggested by smaller case series. Previously, several physical findings and laboratory values were found to be associated with worse outcome in CDC. These were increasing age, immunosuppression, shock requiring vasopressors, peak white blood cell count, peak serum lactate level, hypoalbuminemia, a fall in serum albumin level of >1.1 g/dL at the onset of CDC symptoms, use of 3 or more antibiotics, comorbid disease, previous history of CDC, acute renal failure and hypotension, underlying altered or depressed mental status, abdominal pain or distention, white blood cell count over 20,000/mm^3 or <1500/mm^3 and/or a >10% band forms on the white blood cell differential count, and ascites or pneumatosis coli by abdominal imaging.[9,30–33] Using the APACHE II scale for the same purpose has the advantage of utilizing a well-validated and objective scale that is expected to measure the degree of systemic involvement more reliably compared to the clinical and laboratory values above.

Timing of IVIG infusion remains controversial. Due to the lack of randomized controlled trials, the current practice is guided by expert opinion, leading to wide variations between reports. Since the APACHE II score was positively associated with mortality in the setting of IVIG treatment, the same scale could be used to guide decisions regarding timing of IVIG infusion. Our results suggest that IVIG should be preferentially used while the APACHE II score is still relatively low. This association and the specific APACHE II score at which to initiate or hold treatment need to be validated in the setting of a randomized controlled study before being used in clinical practice.

Although the current study was not designed to test this theory, IVIG could be associated conceptually with treatment success for patients with severe disease that is still restricted to the colon (without other organ dysfunction or at least at an early stage of extracolonic organ failure and thus associated with a low APACHE II score) but not for severe colonic disease with secondary multiple organ failure (high APACHE II score). This may be because colonic disease is toxin-mediated whereas secondary systemic involvement is

TABLE 4. IVIG Treatment Outcome

Patient	Disposition	Clearance of *Clostridium difficile* Colitis?	Days to Resolution
A	Alive	Loose BM persisted but diarrhea resolved 9 days after IVIG.	9
B	Alive	BM became formed and diarrhea resolved 48 hours after IVIG.	2
C	Alive	Diarrhea resolved 20 days post-IVIG infusion. CAT scan: colonic thickening improved.	20
D	Alive	Diarrhea resolved on discharge. Response to IVIG started next day after administration.	18
E	Alive	Diarrhea improved next day after IVIG administration and resolved on discharge.	5
F	Alive	Diarrhea resolved 5 days after IVIG administration.	5
G	Alive	Diarrhea resolved. *C. difficile* test became negative.	13
H	Alive	Diarrhea resolved 2 days before discharge.	15
I	Alive	Diarrhea slowly improved and resolved 4 days before discharge.	7
J	Deceased		
K	Deceased		
L	Deceased		
M	Deceased		
N	Deceased		
O	Deceased		
P	Deceased		
Q	Deceased		
R	Deceased		
S	Deceased		
T	Deceased		
U	Deceased		

Abbreviations: BM, bowel movements; CAT, computerized axial tomography; IVIG, intravenous immunoglobulin.

TABLE 5. IVIG Use for Severe *Clostridium difficile* Colitis: Patient Cohort

Study	Number of Patients	Age (SD) (years)	Male	Female	Severity Definition	IVIG Dose	Days to Resolution	Days IVIG Infused	Alive? (%)	Recurrence
Salcedo et al.[22]	2	63, 64	1	1	Pancolitis or thumbprinting on CAT scan	200–300 mg/kg once	1–2	5–9	100	1 out of 2
McPherson et al.[21]	8	72 (12)	?	?	Pancolitis	200–400 mg/kg twice	2–26	11–65	75	2 out of 6
Juang et al.[25]	18	67 (17.4)	5	13	Modified Rubin et al.[9] criteria	200–300 mg/kg once	?	?	83	?
Hassoun et al.[24]	1	72	1	0	Pancolitis	400 mg/kg once	6	15	100	None
Chandrasekar et al.[23]	1	67	0	1	Shock requiring inotropic support and pseudomembranes on colonoscopy	400 mg/kg for 5 doses	16	35	100	?
This paper	21	68 (16)	7	14	Pancolitis and APACHE II score	300 mg/kg once; 250 mg/kg for 5 doses	2–20	0–25	43	?

Abbreviations: ?, information not available; CAT, computerized axial tomography; IVIG, intravenous immunoglobulin; SD, standard deviation.

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mediated through toxin-induced inflammatory mediators (interleukin-8, macrophage-inflammatory protein-2, substance P, tumor necrosis factor-alpha) released locally in the colon,[34–36] triggering a SIRS and hematogenous translocation of colonic bacteria,[37] both of which are poorly responsive to immunoglobulin infusion. Along the same lines, waiting for failure of conventional therapy before IVIG use might result in IVIG treatment failure because of disease progression and secondary sepsis, at which point no treatment may be effective. No study thus far has addressed this issue specifically.

Overall, the combined cohort of patients with severe CDC treated with IVIG in the literature includes 51 patients (Table 4). The current report contributes 41% of these patients. The patients' average age was 68 years, with a 2 to 1 female-male ratio. The dose of IVIG used varied largely also, with 400 mg/kg being the mode (range, 75–400 mg/kg from 1 to 5 doses). This dose is significantly below the doses used in the treatment of other diseases, like Guillain-Barré syndrome, myasthenia gravis, Kawasaki disease, autoimmune hemolytic anemia, agammaglobulinemia, and hypogammaglobulinemia, where the usual dose is 400 mg/kg for 5 days. The resolution of diarrhea in these cases occurred after an average of 9 (range, 1–42) days. The index hospitalization survival rate varied from 43% to 100%. Patients received standard treatment for an average of 13 (range, 0–65) days before IVIG infusion. Thirty-two of 51 patients survived their illness (63%). Neither total IgG nor anti-toxin A IgG levels were measured in any of the reports. Of the 32 patients who had clinical resolution, 3 (10%) experienced symptoms recurrence in a follow-up period of 1 to 13 months. This number is most probably an underestimation of the true recurrence rate resulting from an incomplete reporting because there was no uniform or active recurrence ascertainment mechanism in any of the studies. The recurrences were at 10, 14, and 30 days posttreatment. Since standard treatment was not discontinued in any of the reports once IVIG was given, the relative contribution and the ideal timing for IVIG infusion are still unclear.

The mechanism of action of IVIG is passive immunization (with anti-toxin A and anti-toxin B antibodies present in the pooled immunoglobulin) of a host who is usually unable to mount an adequate protective immune response.[15,22] IVIG is formed from pooling immunoglobulin from several random donors. It has been shown that many such donors express high anti-toxin A and anti-toxin B antibody serum titers.[38,39] In addition, high levels of anti-toxin A and anti-toxin B antibodies were present in the IVIG preparations and the recipients after infusion.[15–17,22] Although constituting only a small fraction of the total IVIG administered, these antitoxin antibodies are believed to neutralize toxin A and B and help the host recover from the disease. In fact, Babcock et al.[40] used an experimental hamster model of CDC to demonstrate a mortality reduction from 100% to 55% postinfusion of combined anti-toxin A and anti-toxin B antibodies. While some early reports indicated that anti-toxin B antibodies were the major determinants of protection against colitis,[41] later reports correlated disease severity pathologically[42] and clinically[43,44] with anti-toxin A levels. Anti-toxin B antibodies were later shown to play an adjunctive role in conferring immunity against CDC[40,45,46] when added to anti-toxin A antibodies, but not to have any significant role on their own.

However, IVIG has been shown to contain IgG, but not IgA, anti-toxin A and anti-toxin B antibodies while it is only the IgA class of anti-toxin A antibodies, and not the IgG class, that could neutralize toxin A in vitro and in vivo.[47,48] Babcock et al.[40] solved this apparent dilemma by showing that a combination of 3 different monoclonal IgG anti-toxin A antibodies could neutralize toxin A activity in vitro and prevent disease in the hamster model in vivo. Each of the 3 antibodies recognized a different toxin A domain: the first neutralized toxin A enzymatic activity, while the second prevented toxin A binding to its receptor on enterocytes, and the third prevented toxin internalization after binding to the receptor.

Thus, the mechanism of action of IVIG is most likely through the transfer of IgG anti-toxin A antibodies that gain access to the intestinal lumen presumably secondary to inflammation-induced mucosal damage and neutralize toxin A. Transfer of yet undetected IgA anti-toxin A antibodies that prevent toxin A from binding to its receptor is much less likely, although possible.

The present study has limitations. As in all retrospective studies, selection bias was unavoidable. In addition, the decision to initiate IVIG administration was dependent on the attending physician, who also decided the dose, leading to heterogeneity in the total dose of IVIG infused. Such heterogeneity, however, is primarily the result of a lack of a standard dose for IVIG infusion for CDC in the published literature, as reported above. In addition, since IVIG is not yet approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe CDC, standard treatment was not discontinued in any of the reports to date, including ours.

Choosing appropriate controls for patients suffering from severe CDC is challenging. This patient population is usually frail, with severe and multiple underlying diseases. The deteriorating clinical condition (and subsequently the need for multiple antibiotics) may be either the result of or the cause of CDC. Furthermore, IVIG has been in short supply for several years and therefore it has been expensive, making its administration to the number of patients needed to design adequately-powered controlled studies difficult. These are mainly the reasons no randomized, multicenter, placebo-controlled trial on IVIG use in severe CDC has been conducted to date.

Conclusions

In the present study, we report the results of IVIG use for the treatment of 21 patients with severe CDC. This is the

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largest cohort to our knowledge in the literature. Unlike previous studies on the subject, the present report provided 2 scales for disease assessment: the first based on the extent of colonic involvement and the second measuring the severity of systemic involvement using the APACHE II score. The latter was positively associated with mortality in this context. Of the 21 study patients treated with IVIG, only 9 patients (43%) survived their illness. This is the highest reported mortality rate among all studies on this subject so far. Further studies on the ideal timing of IVIG infusion, dose, and patient selection are needed before accepting IVIG as a standard of care for severe CDC treatment. The role of APACHE II score in the decision to use IVIG is promising and should be validated in randomized controlled trials.

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