Original Article

Clinical Predictors of Fulminant Colitis in Patients with *Clostridium difficile* Infection

Mohit Girotra, Vivek Kumar[1], Javaid M. Khan, Pamela Damisse[2], Rtika R. Abraham[2], Vikas Aggarwal[3], Sudhir K. Dutta[4]

Division of Gastroenterology, Department of Medicine, The Johns Hopkins University/Sinai Hospital, Baltimore, [1]Division of Gastroenterology, Department of Medicine, Norwalk Hospital Program/Yale University, Norwalk, CT, [2]Medicine, Johns Hopkins University/Sinai Hospital, Baltimore, MD, [3]Biostatistics, The Johns Hopkins Bloomberg School of Public Health, Baltimore, [4]Department of Medicine, University of Maryland School of Medicine, Baltimore and Division Director of Gastroenterology, Sinai Hospital of Baltimore

Address for correspondence:
Dr. Sudhir K. Dutta, Professor of Medicine, University of Maryland School of Medicine and Division Chief, Gastroenterology, Sinai Hospital of Baltimore, 2411 W. Belvedere Ave, Baltimore, MD, 21215. E-mail: sdutta@lifebridgehealth.org

ABSTRACT

Background/Aim: *Clostridium difficile* infection (CDI) can affect up to 8% of hospitalized patients. Twenty-five percent CDI patients may develop *C. difficile* associated diarrhea (CDAD) and 1–3% may progress to fulminant *C. difficile* colitis (FCDC). Once developed, FCDC has higher rates of complications and mortality. **Patients and Methods:** A 10-year retrospective review of FCDC patients who underwent colectomy was performed and compared with randomly selected age- and sex-matched non-fulminant CDAD patients at our institution. FCDC (n=18) and CDAD (n=49) groups were defined clinically, radiologically, and pathologically. Univariate analysis was performed using Chi-square and Student's t test followed by multivariate logistic regression to compute independent predictors. **Results:** FCDC patients were significantly older (77 ± 13 years), presented with triad of abdominal pain (89%), diarrhea (72%), and distention (39%); 28% had prior CDI and had greater hemodynamic instability. In contrast, CDAD patients were comparatively younger (65 ± 20 years), presented with only 1 or 2 of these 3 symptoms and only 5% had prior CDI. No significant difference was noted between the 2 groups in terms of comorbid conditions, use of antibiotics, or proton pump inhibitor. Leukocytosis was significantly higher in FCDC patients (18.6 ± 15.8/mm^3 *vs* 10.7 ± 5.2/mm^3; P=0.04) and further increased until the point of surgery. Use of antiperistaltic medications was higher in FCDC than CDAD group (56% *vs* 22%; P=0.01). **Conclusions:** Our data suggest several clinical and laboratory features in CDI patients, which may be indicative of FCDC. These include old age (>70 years), prior CDI, clinical triad of increasing abdominal pain, distention and diarrhea, profound leukocytosis (>18,000/mm^3), hemodynamic instability, and use of antiperistaltic medications.

Key Words: *Clostridium difficile*, colitis, fulminant, predictors

Received: 25.08.2011, Accepted: 09.10.2011

How to cite this article: Girotra M, Kumar V, Khan JM, Damisse P, Abraham RR, Aggarwal V, *et al*. Clinical predictors of fulminant colitis in patients with *Clostridium difficile* infection. Saudi J Gastroenterol 2012;18:133-9.

Clostridium difficile has emerged as the most common cause of nosocomial diarrhea in the last half century. In the United States, it affects up to 3 million patients per year.[1-3] It has been established that *C. difficile* can affect up to 8% of all hospitalized patients.[1,4] Majority of the cases are carriers and only 25% develop clinically significant diarrheal disease (*C. difficile* infection [CDI]).[1,4] Medical treatment with antibiotics, such as metronidazole and vancomycin, has been the cornerstone of therapy for CDI for over two decades. The emergence of BI/NAP1/027 strain of *C. difficile* has been associated with increased severity of disease.[5,6]

The progression to fulminant *C. difficile* colitis (FCDC) is quite infrequent (1%–3% of all CDI); however, mortality in this group of patients remains high due to the development of toxic megacolon and colonic perforation. While there is no concrete definition of FCDC, previous investigators have used a number of clinical criteria that include abdominal pain and distention, dehydration, hypotension, oliguria or anuria, high fever, azotemia, and marked leukocytosis in the setting of *C. difficile* infection.[1,3] The development of FCDC requires prompt operative intervention and is associated with high mortality (35%–80%).[1,4,7] We have postulated that recognizing a complete set of clinical risk factors that may predict the development of FCDC can lead to early intervention and presumably reduced morbidity and mortality from FCDC.

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.93820

PATIENTS AND METHODS

A retrospective review of medical records of all the patients admitted to Sinai Hospital of Baltimore, Maryland, USA, between January 2000 and January 2010 was performed.

All adult patients with positive *C. difficile* stool cytotoxin (toxin A and B) and diarrheal illness were included in the initial pool of patients (approximately 2100 patients). The case subgroup comprised all patients who underwent colectomy for FCDC. Exclusion criteria included patients below age 18 years, incomplete medical records, and colectomy for reasons other than FCDC (eg, pelvic malignancy). The control group (n=49) was then picked by random selection from the pool of medically managed CDAD patients. The number of controls was statistically predetermined to attain good power (power and sample size calculator, Version 3.0.17).

Definitions

FCDC was defined as systemic inflammatory response (presence of two or more of the following: Temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ lower than 32 mmHg, white blood cells >12,000 μL or lower than 4000/μL, or 10% band cells), hypotension, or need for volume resuscitation or vasopressors in the setting of documented CDI by stool cytotoxin assay. This group also includes patients with radiographic evidence of severe colitis and/or the presence of pseudomembranes on colonoscopy. CDAD was defined as diarrheal disease with the presence of fecal *C. difficile* cytotoxin, but absence of above-mentioned features of systemic inflammatory response, or hemodynamic instability.

A detailed review of medical records was carried out in patients who underwent colectomy for FCDC (n=18), and compared with a group of randomly assigned, medically managed patients with CDAD (n=49). Several clinical, laboratory, and radiographic features that had been previously linked to fulminancy in case reports and also additional prognostic markers, which we thought were important from our experiences were collected. The data points recorded included the following:

1. Patient's age, recent surgical procedure, recent and/or ongoing proton pump inhibitor (PPI) use and antibiotic use, recent CDI (within 1 month), and other medications, including anti-peristaltics.
2. Symptoms: Abdominal pain, distention, diarrhea, fever, vomiting, constipation, and decreased urinary output.
3. Laboratory features: White blood cell (WBC) count on admission and either 48 h after admission or immediately prior to colectomy; biochemical profile at admission and prior to surgery; serum creatinine, lactate, and albumin.
4. Comorbid illnesses (ie, diabetes mellitus, cancer, renal insufficiency/end-stage renal disease), intravenous immunoglobulin (IVIg) therapy, immunosuppressive therapy (including chemotherapy, steroids, tacrolimus, cyclosporine).
5. Hemodynamic status: Tachycardia (heart rate>100 beats/min), hypotension (systolic blood pressure<90mmHg), tachypnea (respiratory rate>18/min), need for ICU admission and vasopressors.
6. Radiographic and colonoscopic findings (including pseudomembranes, megacolon, perforation).

Statistics

All data were recorded on MS-Access data sheet in a HIPAA protective manner and analyzed using SPSS. All results are reported in descriptive statistics and expressed as mean±SD for continuous values and median for nominal values, unless otherwise specified. Univariate analysis was performed using Chi-square test for categorical variables and Student's t test for continuous data. Multivariate logistic regression was later carried out to include all variables with significant P value in the original model to predict independent predictors. Observed differences were considered statistically significant at P value <0.05.

RESULTS

Of all the patients admitted to our hospital with positive CDI during a 10-year period, 49 patients required colectomy for FCDC. Ten cases were excluded due to lack of adequate clinical, biochemical, and radiologic data. Another 21 patients had other associated reasons for colectomy, such as ovarian or other pelvic malignancies, and were excluded. Some of these patients developed CDI during hospital stay and underwent colectomy along with pelvic exenteration surgery. In these patients, the reason for colectomy was primarily a pelvic malignancy and CDI was deemed to be secondary. Thus, the final case population included 18 patients, who underwent colectomy primarily for FCDC.

FCDC patients were significantly older (mean age 77 ± 13 years) as compared with CDAD group (65 ± 20 years), without any significant difference in reference to gender or ethnicity [Table 1]. At the time of initial presentation, three clinical features were significantly higher (P<0.05) in FCDC group as compared with controls—abdominal pain (89%), diarrhea (72%), and distention (39%) [Figure 1]. No patient in either group demonstrated any features of peritonitis. In addition, FCDC patients had significantly higher WBC (18.6 ± 15.8/mm^3), hemodynamic instability in terms of tachycardia, hypotension, and tachypnea at admission. The mean body temperature appeared to be lower in FCDC group, but the difference was not statistically significant. Similarly, the frequency of renal insufficiency and end-stage

renal disease (ESRD) was not different in the two groups. Furthermore, no specific condition was found to be more common in FCDC group when the comorbid conditions were compared in the two groups [Table 1].

Twenty-eight percent FCDC patients had CDI in the previous 1 month, which was significant when compared with CDAD group ($P<0.05$). In terms of medications, antibiotic use was higher in FCDC (72%) than in CDAD group (51%), however, this difference failed to reach the mark of statistical significance [Figure 2]. There was no significant difference noted in PPI use between the two groups (67% *vs* 59%, P=ns). However, a significantly high number of FCDC patients had been on antiperistaltic medications than CDAD patients (56% *vs* 22%, $P=0.01$) [Figure 2].

FCDC patients had a significantly longer hospital stay along with greater likelihood of receiving ICU care and vasopressors support ($P<0.001$). Colonoscopy was performed on 8/18 (44.4%) patients in FCDC group, and toxic megacolon (17%) was noted to be significantly higher ($P<0.05$) as compared with CDAD group [Table 2]. Six out of 18 patients in FCDC group were taken for surgery immediately after admission due to severe hemodynamic instability, and the other 12 cases were treated medically first, and they underwent colectomy following the failure of medical therapy. Patients in the CDAD group were treated with metronidazole and vancomycin in equal proportions, and in FCDC group, vancomycin (58%) was the more frequently used drug. 2/18 (11%) patients died

Table 1: Demographic characteristics, co-existing medical conditions, laboratory and hemodynamic parameters at admission in patients with FCDC and CDAD

	FCDC (*n*=18) (%)	CDAD (*n*=49) (%)	*P* value
Age (years)			
Mean ± SD	77 ± 13	65.5 ± 20	**0.03**
Gender			
Male	4 (22.2)	19 (38.8)	0.21
Female	14 (77.8)	30 (61.2)	
Ethnicity			
Caucasian	12 (66.7)	39 (79.6)	0.05
Black	4 (22.2)	10 (20.4)	
Others	2 (11.1)	0	
Coexisting medical conditions			
Diabetes mellitus	3 (16.67)	5 (10.2)	0.47
Chronic obstructive pulmonary disease	2 (11.1)	2 (4.1)	0.28
Cirrhosis	0	0	-
Immunosuppression	1 (5.6)	4 (8.2)	0.72
Inflammatory bowel disease (IBD)	2 (11.1)	0	**0.01**
Intravenous immunoglobulin (IVIg)	1 (5.6)	1 (2.0)	0.45
Malignancy	7 (38.9)	14 (28.6)	0.42
Acute renal failure	6 (33.3)	7 (14.3)	0.08
End-stage renal disease (ESRD)	1 (5.6)	0	0.09
Complete blood count (Mean±SD)			
White cell count (×10^3)	18.6 ± 15.8	10.7 ± 5.2	**0.04**
Hematocrit (in %)	34.7 ± 4.0	34.8 ± 6.1	0.94
Platelets (×10^5)	297.5 ± 102.5	219.6 ± 103.0	**0.009**
Complete metabolic profile (Mean±SD)			
Sodium	138.2 ± 4.4	138.4 ± 3.7	0.87
Potassium	3.7 ± 0.75	3.9 ± 0.54	0.37
Creatinine (mg/dL)	1.3 ± 1.3	1.14 ± 0.35	0.55
Albumin (mg/dL)	3.2 ± 0.8	3.7 ± 0.9	0.09
Urine output (mL/day) (Mean±SD)	1036.4 ± 613.6	1337.8 ± 1030	0.28
Vital signs (Mean±SD)			
Temperature>38.3	34.5 ± 2.6	36.9 ± 0.8	0.25
Heart rate>100 bpm	94.8 ± 24.8	76.7 ± 17.9	**0.009**
Systolic B*P*<90 mmHg	115.7 ± 21.7	133.3 ± 23.5	**0.007**
Respiratory rate>20/min	22.2 ± 4.9	19.2 ± 3.9	**0.03**

CDAD: *Clostridium difficile* associated diarrhea, ESRD: End-stage renal disease, FCDC: Fulminant *C. difficile* colitis, IBD: Inflammatory bowel disease, IVIg: Intravenous immunoglobulin, SD: Standard deviation. Values in bold are significant

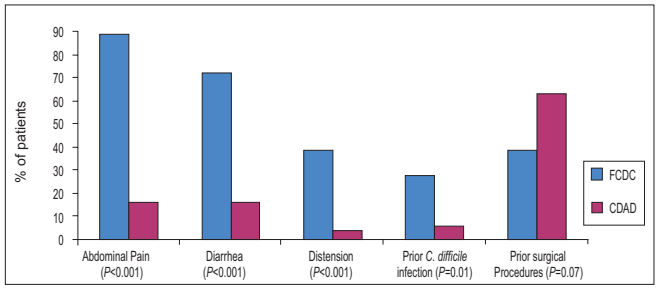

Figure 1: Barographic comparison of presenting symptoms in fulminant *Clostridium difficile* colitis (FCDC) and *C. difficile* associated diarrhea (CDAD) groups. Patients in FCDC group have significantly higher abdominal pain, distention, and diarrhea when compared with CDAD patients. Also, there is a significant history of prior *C. difficile* infection in FCDC subgroup

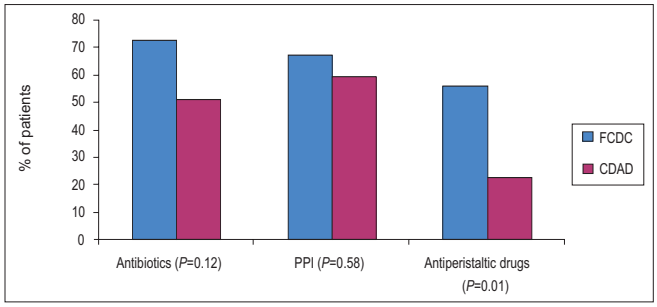

Figure 2: Barograph demonstrating the effect of different medications on the development of fulminant *Clostridium difficile* colitis (FCDC). There is no significant difference between FCDC and *C. difficile* associated diarrhea groups in terms of antibiotic or proton pump inhibitor use, but a significantly higher use of antiperistaltic medications in FCDC group

in our FCDC group, both due to septic shock. There were no deaths in CDAD group.

A subgroup analysis was attempted among FCDC patients (n=18) comparing parameters at admission and subsequently before colectomy [Table 3]. There was an appreciable increase in white blood cell count from 18.6 ± 15.8/mm^3 to 26.22 ± 17.3/mm^3; however, it failed to reach the mark of statistical significance. There was a significant drop in serum albumin and platelets among FCDC patients during this period of trial of medical therapy. There was no other difference in metabolic or renal parameters among the two groups. A multivariate logistic regression model was created using all significant variables, and old age (>70 years), abdominal pain, and leukocytosis >18,000/mm^3 were separated out as independent predictors of fulminancy (Goodness of fit P=0.40).

Table 2: Hospital course and treatment outcomes of patients with FCDC and CDAD

	FCDC (%)	CDAD (%)	*P* value
Total hospital stay (days) (Mean±SD)	19 ± 10.9	6.3 ± 5.5	**<0.001**
Patients requiring ICU care	14 (77.8)	5 (10.2)	**<0.001**
Pressors requirement	6 (33.3)	2 (4.1)	**<0.001**
Intubation requirement	7 (38.9)	2 (4.1)	**<0.001**
Use of total or peripheral parenteral nutrition (TPN/PPN)	13 (72.2)	0	**<0.001**
Colonoscopy done	8 (44.4)	7 (14.3)	0.009
Pseudomembranes	2 (11.1)	0	0.15
Megacolon	3 (16.7)	0	**0.003**
Perforation	3 (16.7)	0	**0.05**
Medical treatment attempted	12 (66.7)	49 (100)	**<0.001**
Antibiotics			
Metronidazole	5 (41.7)	25 (51)	—
Vancomycin	7 (58.3)	24 (49)	—
Duration of treatment (in days) (Mean ± SD)	5.6 ± 6.1	15.6 ± 2.9	**<0.001**
Death	2 (11.1)	0	**0.02**

CDAD: *Clostridium difficile* associated diarrhea, FCDC: Fulminant *C. difficile* colitis, SD: Standard deviation, TPN/PPN: Total/peripheral parenteral nutrition. Values in bold are significant

Table 3: Clinical and laboratory features in patients with FCDC at the time of admission and prior to surgery

	FCDC at admission (Mean±SD)	FCDC before surgery (Mean±SD)	*P* value
Complete blood count			
White cell count (×10^3)	18.6 ± 15.8	26.22 ± 17.3	0.14
Hematocrit (%)	34.7 ± 4.0	31.8 ± 5.7	0.09
Platelets (×10^5)	297.5 ± 102.5	211 ± 126.3	0.03
Complete metabolic profile			
Sodium	138.2 ± 4.4	139.1 ± 4.1	0.56
Potassium	3.7 ± 0.75	3.8 ± 0.54	0.80
Creatinine (mg/dL)	1.3 ± 1.3	1.14 ± 0.35	0.55
Albumin (mg/dL)	3.2 ± 0.8	2.1 ± 1.1	0.03
Vital signs			
Temperature	34.5 ± 2.6	36.7 ± 1.2	0.29
Heart rate	94.8 ± 24.8	101.3 ± 10.7	0.31
Systolic blood pressure	115.7 ± 21.7	124.8 ± 22.0	0.22
Respiratory rate	22.2 ± 4.9	19.4 ± 4.1	0.08

FCDC: Fulminant *C. difficile* colitis

DISCUSSION

Available clinical and epidemiologic data suggest that the incidence of CDI is clearly increasing in hospitalized patients and affects more than 3 million patients every year in the United States.[1,3,4,8] The severity of CDI also appears to be on the rise with overall incidence of FCDC being in the range of 1–5%.[4,6,9] Some studies have reported a high mortality in FCDC patients ranging from 34% to 80%.[4,7,10,11] This increase in mortality rate in FCDC group can be attributed to several factors, which include emergence of new virulent strain BI/NAP1/027,[6] higher frequency of antibiotic resistance, older patient population, associated comorbid conditions, such as renal failure, congestive heart failure, immunosuppression, and surgical intervention with total and subtotal colectomy.

We have postulated that ability of identification of clinical and laboratory features associated with the development of FCDC may be a significant step toward diminishing the associated mortality.[3,4] A timely surgical intervention in FCDC patients is shown to have up to 78% reduction in mortality.[12] Current clinical guidelines reserve surgical intervention for patients with fulminant colitis associated with multisytem organ failure and shock. Specific indications for colectomy include organ failure, shock, requirement for vasopressors, worsening CT scan findings in the face of medical management, signs of peritonitis, or lack of response to maximal medical management by 72 h.[13] Subtotal colectomy and ileostomy in this setting has a reported mortality of 35–57%, and delayed intervention was found to be the most important factor associated with increased mortality in FCDC.[13,14] Early identification of clinical predictors of fulminant colitis can presumably reduce the morbidity and mortality in these patients.

In our study, the mean age of patients with FCDC was significantly higher (77 ± 13 years) as compared with CDAD patients. Our results concur with previous studies reporting old age to be a predictor of fulminancy in *Clostridium difficile* patients.[1,3,15] The reasons include associated comorbidities with compromised and/or defective immune response to *C. difficile* toxins in this group of patients. We have observed that our FCDC patients presented with a triad of abdominal pain

(89%), diarrhea (72%), and distention (39%) [Figure 1]. Frequency of these 3 symptoms was significantly higher in FCDC than in the CDAD group. Furthermore, out of all the patients with positive clinical triad (7 patients), 72% belonged to the FCDC group. Although diarrhea is considered a hallmark of CDI, it is noteworthy that its absence or resolution does not rule out the development of FCDC completely. Five patients in our FCDC group presented with nondiarrheal disease. It is noteworthy that absence of diarrhea in CDI could be secondary to severe colonic dysmotility or effect of certain medications. Disappearance of diarrhea in CDI should be a warning sign for the development of fulminancy.[11,16]

Hemodynamic abnormalities and renal dysfunction have been used in the assessment of severity of CDI in patients. In our study, hemodynamic instability at admission was an additional important marker of fulminancy. We noted that tachycardia, tachypnea, and hypotension were significantly more common in FCDC as compared with CDAD patients. Development of these features in patients with CDI should alert the physicians to greater likelihood of progression to fulminancy.[15] These patients were deemed more sick compared with CDAD patients and often ended up receiving ICU care and vasopressors. Interestingly, fever was neither a major presenting symptom, nor a marker of fulminancy in our study. A possible explanation for this finding could be the inability of older and sicker patients to mount an identifiable febrile response. In addition, Seder *et al*. suggested renal insufficiency as independent predictors of fulminancy.[4] In our study, however, the frequency of ESRD or renal insufficiency was not statistically different in the two groups. Furthermore, FCDC has previously been noted to occur more frequently in immunocompromised patients on chemotherapy or after transplantation/surgery.[5,17] Conversely, in our study, immunosuppression was not found to be more common among FCDC patients. A similar observation has previously been reported by Keven *et al*. who did not find significant increase in *C. difficile* colitis in solid organ transplant patients.[18] Additionally, in our study, there was no particular relationship noted between comorbid conditions (such as diabetes, immunosuppression, ESRD, and others) and development of FCDC.

Leukocytosis has been a well-recognized hallmark of CDI, even in the absence of diarrhea.[2,6,8,9,17,19] In our study, patients with FCDC had much higher WBC count at admission (18.6±15.8/mm^3) as compared with CDAD group, suggesting that severe leukocytosis maybe a marker of fulminancy. This observation is in conformity with other studies that suggested substantial leukocytosis as useful prognosticator of fulminancy.[1,15] The precise mechanism of leukemoid reaction in patients with FCDC is still unclear but may be related to significant systemic inflammatory response causing bone marrow stimulation.[16] Systemic inflammatory states, such as CDI are associated with elevated levels of G-CSF, which presumably release neutrophils and their precursors from the bone marrow causing leukocytosis.[20] Furthermore, the WBC count in FCDC patients continued to rise (26.22 ± 17.3/mm^3; P=0.07) when followed until the point of surgery. Nevertheless, this change of leukocyte count failed to reach statistical significance (P=0.07) due to small sample size. In addition to leukocytosis, Greenstein *et al*. reported that patients with IBD and those receiving IVIg treatment had a higher frequency of development of fulminancy.[1] In our study, 2 patients in FCDC group had IBD and only 1 received IVIg therapy. Due to limited number of IBD cases in our study population, it is not possible for us to make any definitive statement about the impact of IBD/IVIg on FCDC. Ours is a study representing community population where incidence of IBD and IVIg treatments is not very high.

One of the most important findings in our study is that a large number (56%) of FCDC patients were on antiperistaltic agents, such as narcotics or anticholinergics upon admission. They were taking these prescriptions from their primary care provider for various pain-related reasons. Administration of these medications can potentially lead to the development of clinical features of FCDC due to decreased peristalsis. This could probably be a factor tipping these patients toward appearance of fulminant disease by affecting peristalsis, reducing bacterial clearance and cascade of other changes causing colonic dilation. Narcotics and anticholinergics should be administered with caution and preferably avoided in elderly patients, suspected of having CDI. Furthermore, one of the most well-reported risk factors for development of CDI and its recurrence is prior antibiotic use.[21,22] However, in our study there was no evidence for increase in fulminancy with current or prior antibiotic use. Several studies have also suggested an association of PPI use with incidence as well as recurrence of CDI,[23,24] which is presumed to be due to chronic acid suppression leading to alteration of gut flora.[25] However, in our study PPI use was not statistically different between the two groups, suggesting that acid suppression alone may not be the only critical factor in the development of fulminancy in patients with CDI. This is in accordance with a study by Wilcox *et al*. that did not associate PPI use with CDI.[26] This was later tested *in vitro* by Nerandzic *et al*. who showed that *C. difficile* spores survived in acidic gastric contents and did not undergo germination and outgrowth in PPI-treated gastric contents due to lack of essential germinants, such as taurocholic acid, hence concluding that PPIs in stomach do not contribute to pathogenesis of CDI.[27]

Box 1: Summary of red flags for development of fulminant *Clostridium difficile* colitis

Age>70 years
Presenting symptoms: Triad of abdominal pain, diarrhea, and distention
Signs: Tachycardia (heart rate>100 beats/min), tachypnea (respiratory rate>20 respirations/minute) or hypotension (systolic blood pressure<90 mmHg)
Recent *C. difficile* infection
Use of antiperistaltic medications (narcotics or anticholinergics)
White blood cell count>18,000/mm^3
Radiology studies suggestive of megacolon or perforation

In terms of hospital course, it is apparent that FCDC patients had a significantly longer duration of hospital stay, greater likelihood of ICU admissions, and higher vasopressors requirement. All these observations suggest the degree of severity in FCDC patients compared with CDAD patients. Radiologic imaging in FCDC patients showed significantly higher megacolon (17%) and perforations (17%) compared with the CDAD group, due to greater severity of colitis, in accordance with other studies.[11,28] There were 2 deaths in our FCDC group and none in CDAD group, and this mortality rate for our surgical subgroup (11%) was less than the range reported by other authors.[3,7,11]

In summary, our observations suggest a number of clinical and laboratory features in patients with CDI, which may predict the development of fulminant disease [Box 1]. Elderly patients (>70 years) with prior *C. difficile* illness, presenting with a triad of increasing abdominal pain, distention, and diarrhea, along with profound leukocytosis (>18,000/mm^3) are at a high risk of developing fulminant colitis. The development of hemodynamic instability (tachycardia, tachypnea, and hypotension) in such patients further raises the possibility of development of fulminancy. Use of antiperistaltic medications is likely to worsen the clinical condition by precipitating toxic megacolon and possibly leading to perforation. These features can be considered as red flags for development of FCDC. Close monitoring of these factors may be critical in reducing mortality by providing timely aggressive medical and surgical intervention. A controlled prospective study on larger patient population is needed to confirm these observations.

REFERENCES

1. Greenstein AJ, Byrn JC, Zhang LP, Swedish KA, Jahn AE, Divino CM. Risk factors for the development of fulminant *Clostridium difficile* colitis. Surgery 2008;143:623-9.
2. Barbut F, Corthier G, Charpak Y, Cerf M, Monteil H, Fosse T, *et al*. Prevalence and pathogenicity of *Clostridium difficile* in hospitalized patients: A French multicenter study. Arch Intern Med 1996;156:1449-54.
3. Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, *et al*. Fulminant *Clostridium difficile* colitis: Patterns of care and predictors of mortality. Arch Surg 2009;144:433-9.
4. Seder CW, Villalba MR Jr, Robbins J, Ivascu FA, Carpenter CF, Dietrich M, *et al*. Early colectomy may be associated with improved survival in fulminant *Clostridium difficile* colitis: An 8-year experience. Am J of Surg 2009;197:302-7.
5. Efron P, Mazuski JE. *Clostridium difficile* colitis. Surg Clin North Am 2009;89:483-500.
6. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, *et al*. A predominantly clonal multi-institutional outbreak of *Clostridium difficile* associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442-9.
7. Byrn JC, Maun DC, Gingold DS, Baril DT, Ozao JJ, Divino CM. Predictors of mortality after colectomy for fulminant *Clostridium difficile* colitis. Arch Surg 2008;143:150-4; discussion 155.
8. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short stay hospitals, 1996-2003. Emerg Infect Dis 2006;12:409-15.
9. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. Clin Infect Dis 2008;46 Suppl 1:S12-8.
10. Wysowski DK. Increase in deaths related to enterocolitis due to *Clostridium difficile* in the United States, 1999-2002. Public Health Rep 2006;121:361-2.
11. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for *Clostridium difficile* colitis. Dis Colon Rectum 2004;47:1620-6.
12. Lamontagne F, Labbe AC, Haeck O. Impact of emergent colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by hypervirulent strain. Ann Surg 2007;242:267-72.
13. Jaber MR, Olafsson S, Fung WL, Reeves ME. Clinical review of the management of fulminant *Clostridium difficile* infection. Am J of Gastroenterol 2008;103:3195-203.
14. Hall JF, Berger D. Outcome of colectomy for *Clostridium difficile* colitis: A plea for early surgical management. Am J Surg 2008;196:384-8.
15. Dallal RM, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, *et al*. Fulminant *Clostridium difficile*: An underappreciated and increasing cause of death and complications. Ann Surg 2002;235:363-72.
16. Grundfest-Broniatowski S, Quader M, Alexander F, Walsh RM, Lavery I, Milsom J. *Clostridium difficile* colitis in the critically ill. Dis Colon Rectum 1996;39:619-23.
17. Pépin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, *et al*. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991-2003: A changing pattern of disease severity. CMAJ 2004;171:466-72.
18. Keven K, Basu A, Re L, Tan H, Marcos A, Fung JJ, *et al*. *Clostridium difficile* colitis in patients after kidney and pancreas-kidney transplantation. Transpl Infect Dis 2004;6:10-4.
19. Wanahita A, Goldsmith EA, Marino BJ, Musher DM. *Clostridium difficile* infection in patients with unexplained leukocytosis. Am J Med 2003;115:543-6.
20. Bagby GC. Leukopenia and leukocytosis. In: Goldman L, Bennett JC, editors. Cecil's textbook of medicine. 21st ed. Philadelphia: W.B Saunders Co; 2000. p. 919-33.
21. Gerding DN, Johnson S, Peterson LR. *Clostridium difficile* associated diarrhea and colitis. Infect Control Hosp Epidemiol. 1995; 16:459-77.
22. Jaber MR, Olafsson S, Fung WL, Reeves ME. Clinical review of management of fulminant *Clostridium difficile* infection. Am J Gastroenterol 2008;103:3195-203.
23. Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. Aliment Pharmacol Ther 2009;29:626-34.
24. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric-acid suppressive

agents and the risk of community acquired *Clostridium difficile* associated disease. JAMA 2005;294:2989-95.
25. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, *et al*. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. Arch Intern Med 2010;170:784-90.
26. Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated *Clostridium difficile* infection. J Antimicrob Chemother 2008;62:388-96.
27. Nerandzic MM, Pultz MJ, Donskey CJ. Examination of potential mechanisms to explain the association between Proton pump inhibitors and *Clostridium difficile* infection. Antimicrob Agents Chemother 2009;53:4133-7.
28. Rubin MS, Bodenstein LE, Kent KC. Severe *Clostridium difficile* colitis. Dis Colon Rectum 1995;38:350-4.

Source of Support: Nil, **Conflict of Interest:** None declared.