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ORIGINAL ARTICLE

C. difficile Colitis—Predictors of Fatal Outcome

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Abstract
Purpose *Clostridium difficile* colitis (CDC) has a clinical spectrum ranging from mild diarrhea to fulminant, potentially fatal colitis. The pathophysiology for this variation remains poorly understood. A total abdominal colectomy may be lifesaving if performed before the point of no return. Identification of negative prognostic factors is desperately needed for optimization of the clinical and operative management.
Methods In-patients with CDC between 1999 and 2006 were identified through the discharge database (ICD-9: 008.45). Of these, patients with positive ELISA toxin or biopsy were included. Excluded were ELISA-negative patients. Data collected included general demographics, underlying medical conditions, APACHE II score, clinical and laboratory data, and duration of the medical treatment. Mortality and cure were the two endpoints. Regression analysis was used to identify parameters associated with mortality.
Results Three hundred ninety-eight patients (mean age 59, range 19–94) with CDC were analyzed. Fourteen patients (3.52%) underwent surgery. Mortality in the cohort was 10.3% (41/398 patients). Patients with fatal outcome had a longer pre-CDC hospital stay (11 vs. 6 days). Mortality was significantly ($p<0.05$) associated with a higher APACHE II score, a higher ASA class, a lower diastolic blood pressure, preexisting pulmonary and renal disease, use of steroids, evidence of toxic megacolon, higher WBCs, and clinical signs of sepsis and organ dysfunction (renal and pulmonary). Parameters without significant difference ($p>0.05$) included patient age, albumin, clinical presentation/examination parameters, and transplant status, other than the mentioned comorbidities. Of the 41 fatal outcomes, five patients (12.2%) underwent surgery, and 36 did not (87.8%). Mortality rate of the surgical group was 35.7% (four out of 14 patients). Comparison of the fatalities not undergoing surgery with the survivors revealed decreased clinical signs, suggesting a masking of the disease severity.
Conclusions Our study identified several clinical factors, which were associated with mortality from CDC. Future clinical studies will have to focus on the disease progression and the fatalities occurring either without an attempt for or despite surgical intervention, as an earlier intervention might have proven lifesaving.

Keywords *C. difficile* colitis · Pseudomembranous colitis · Mortality · Predictors · Surgery · Colectomy

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Abbreviations

ASA	American Society of Anesthesiologists
CDC	*C. difficile* colitis
LOS	Length of hospital stay
WBC	White blood cells

Introduction

Clostridium difficile infection has been associated with a wide spectrum of clinical presentations ranging from mild diarrhea to fulminant and potentially fatal toxic colitis.[1,2]

Alteration of the colonic flora as a result of antibiotic medications or other host factors allows for selection and overgrowth of toxin-producing *Clostridium* strains.[3] The severity of symptoms presumably is a function of the balance between bacterial virulence and host defense mechanisms.[4] The treatment of *C. difficile* colitis (CDC) in the majority of patients is conservative. Common measures include discontinuation of the causative antibiotics (if possible), administration of toxin binders (e.g., cholestyramine), and administration of antibiotics against the *C. difficile*. These antibiotics are given via oral–gastric (e.g., vancomycin), for some drugs (metronidazole) via oral or intravenous route.[5] A relatively small group of individuals with aggressive fulminant disease, however, will only have a chance to survive if they undergo an urgent radical surgery (total abdominal colectomy).[6,7]

The factors leading to these two stark contrasting forms of the same disease continue to be poorly understood. Several recent reports from the USA, Canada, and Europe have documented a growing numbers of both community- and hospital-acquired regional outbreaks of *C. difficile* colitis, which led to the identification of different virulence subtypes.[4,6,8–10] The emergence of hypervirulent strains has been associated with a higher incidence of the severe form of the disease with increased 30-day mortality due to reduced responsiveness to antibiotics and a higher incidence of toxic megacolon, intestinal perforation, and of the rate of needed colectomy.[6,9,11]

Insights into the pathophysiology of fulminant CDC remain sparse, and the current knowledge of predictive parameters for a fatal outcome is limited.[12] A total abdominal colectomy with end ileostomy may be lifesaving if performed before the point of no return has been crossed[7]; however, the decision for recommending such a big operation with an ostomy before a patient is visibly crashing remains in many instances an intellectual and emotional challenge. The literature with reports of high morbidity and mortality associated with the surgical treatment for fulminant colitis is counterproductive in that situation,[12] as these unreflected statements with wrongly superficial conclusions risk pushing physicians into a harmful direction. However, a total abdominal colectomy or even more extensive resections are very safe procedures under different circumstances.[13] The adverse outcome in the setting of fulminant colitis therefore seems to rather reflect the impact of inadequate timing with a delay of surgery rather than a risk of the surgery as such.[13–16] Hence, identification of negative prognostic factors is desperately needed for optimization of the decision-making process for the clinical and operative management.

In the current communication, we attempted to address some of these issues by reviewing all cases of *C. difficile* colitis at our 293-bed institution within an 8-year period. In contrast to other authors, we did not limit our study population to just the fulminant cases or the surgical patients but included all patients with a confirmed CDC. The objectives of our analysis were to develop a better understanding of the dynamics of unfavorable outcomes of CDC with and without surgery and to define predictive clinical parameters and constellations associated with failure of surgical or non-surgical management and with mortality.

Material and Methods

Patients who were treated for acute *C. difficile* colitis within the 8-year period between January 1999 and December 2006 at the USC University Hospital were identified from the inpatient discharge database and retrospectively analyzed. Included were all inpatients with an ICD-9 code of "*C. difficile* colitis" (008.45), whose *C. difficile* diagnosis was confirmed by means of a positive toxin ELISA, or a biopsy consistent with pseudomembranous colitis. Excluded were patients whose *C. difficile* was only diagnosed on a clinical basis but who remained test negative. After identification of the patients, the full medical records were reviewed by a group of three physicians (HD, ES, and CGR) using our institutional electronic medical record (Electronic Patient Folder, version 4.50.4, HBO & Company). Data were entered into a datasheet that had been generated with Microsoft Access XP and Excel XP. Among 124 parameters recorded were patient demographics, symptoms and duration of symptoms, underlying disease and comorbidities, clinical signs, white blood cells, ASA class, APACHE II scores, medical and surgical treatments, complications, outcome during the hospital stay, as well as other clinical, imaging, and laboratory data. For serial datapoints, the maximum value within the period related to the CDC treatment was used for data analysis.

The study protocol and data collection were approved by the Institutional Review Board of the University of Southern California and were compliant with HIPAA regulations.

Statistical Analysis

Results were reported in descriptive statistics and expressed as mean±standard deviation for continuous values, as median for nominal values (e.g., ASA). Statistical analysis was performed with SigmaStat software (Version 3.11, Systat Software Inc, Richmond, CA, USA) to compare groups of patients. The X^2 test or Fisher's exact test was used for nominal variables, the unpaired Student's t test or Mann–Whitney rank sum test for comparison of two groups, and one-way analysis of variance with Mann–Whitney rank sum test and Dunn's test as a post hoc test for comparison of more than two groups. Multivariate logistic

regression analysis was used to determine the predictive impact of multiple factors on mortality. Observed differences were considered statistically significant if $p<0.05$.

Results

Patient Characteristics

Data from 398 patients (190 men, 208 women) with a mean age of 59.4±16.3 years (range 19–94 years) were included in the study analysis. Based on the inclusion criteria, 97% of patients were toxin positive, and the remaining 3% were diagnosed by means of the pathology. Patient characteristics of the whole patient collective as well as of the four subgroups (survivors vs. fatal, medical vs. surgical) are shown in Table 1. A severe or fulminant/toxic course, defined as a presentation requiring surgery or resulting in death, occurred in 50 out of 398 patients (12.6%). The subgroups were equal and represented similar patients except for their size and the ASA classification.

Surgical Approach

Of the 14 surgical patients, 11 patients (78.6%) underwent a subtotal colectomy with diversion, one a colectomy without diversion, one underwent colostomy alone, and one underwent an exploration with colotomy and washout. Mortality in the subtotal colectomy with ileostomy group was 36.4% (four patients), while mortality with the other surgeries were 33.3% (one patient). It is of note that the patient treated only with a colonic washout did very well after surgery.

Mortality and Predictive Parameters

The whole cohort had a mortality of 41 out of 398 patients (10.3%). In five of them (12.2%), curative surgery was attempted but failed, resulting in a surgical mortality of 35.7% (five out of 14 patients who underwent surgery for toxic/fulminant CDC).

Direct comparison of survivors with the patients who died revealed a number of significant differences (as shown in Table 2) in both preexisting factors and parameters related to the acute presentation. In the survivors, most notably, the length of hospital stay prior to the diagnosis of CDC was significantly shorter, and the frequency of steroid use and renal or respiratory insufficiency were lower. The non-survivor group had statistically significantly higher APACHE II scores, a higher ASA class, lower diastolic blood pressures, a higher mean WBCs, and a higher percentage of them revealed clinical signs of sepsis and organ dysfunction (renal, pulmonary). Regression analysis confirmed the disease scores as well as preexisting renal and pulmonary dysfunction and steroid use as independent risk factors for mortality.

Correlation of the mortality with four ranges of WBCs is shown in Fig. 1, while the differences were not significant, and in the same range between WBCs <10, 10–15, and 16–20, there was a sharp increase of the mortality for WBCs >20. Figure 2a, b shows the impact of the ASA class and the APACHE II score on the mortality and the needed surgery.

A number of other examined factors (including the patients' age), however, did not reveal any significant difference (see Table 2). While steroid use remained associated with poor outcome on multivariate regression analysis, post-transplant status, other forms of immunosuppression or a history of cancer or chemotherapy did not show an impact on outcome.

Thirty-six of the 41 patients (87.8%) who died were not offered surgical treatment for various reasons, not all of which were apparent on the retrospective data review. This subgroup of severely ill patients represents the major target of the attempt to define predictors of negative outcome, as a

Table 1 Patient Characteristics

	Survivors medical	Survivors operative	Fatal medical	Fatal operative	Total	p<0.05
Number of patients (%)	348 (87.4)	9 (2.3)	36 (9.0)	5 (1.3)	398	-
Male/Female	165/183	5/4	17/19	3/2	190/208	-
Age	59±16	57±21	61±15	66±17	59±16	no
ASA [median]	3	3	4	3	3	yes[1]
% of patients with CDC after previous surgery	50.9	44.4	50.0	60.0	50.8	no
LOS before diagnosis of CDC	10.7	5.2	15.6	15.0	11.1	no

[a] Fatal med vs. SV surg; Fatal med vs. SV cons (Mann–Whitney rank sum test).

Table 2 Comparison of Survivors and Non-survivors

Factors	Parameters	Survivors (n=357)	Non-survivors (n=41)	p value
Preexisting	Pre-CDC LOS [days]	11.2	16.4	0.013
	Renal Insufficiency [%]	17.9	36.6	0.009
	Steroid use [%]	21.0	41.5	0.006
	Cancer [%]	29.4	19.5	0.251[a]
	COPD [%]	12.3	19.5	0.294[a]
	Diabetes [%]	31.1	43.9	0.138[a]
	Hypertension [%]	46.8	51.2	0.708[a]
	CAD [%]	21.8	24.4	0.863[a]
	Immunosuppression [%]	33.1	39.0	0.559[a]
	Transplant [%]	19.0	26.8	0.329[a]
	Chemotherapy [%]	11.2	4.9	0.327[a]
	Patient age [years]	59.0±16.4	62.4±15.2	0.097
Scores	ASA [median]	3	4	<0.001[b]
	APACHE II	6.1	8.1	0.006
Clinical signs	Diastolic BP	68.9	61.9	0.009
	Respiratory rate	20.1	22.9	0.034
	Sepsis [%]	2.0	17.1	<0.001
	Organ failure [%]	22.4	68.2	<0.001
	Renal failure [%]	16.0	43.9	<0.001
	Respiratory Failure [%]	5.0	39.0	<0.001

[a] Low power due to low number of patients detected in study

[b] Mann–Whitney rank sum test

timely decision for surgery might potentially have resulted in a different outcome. We therefore compared this group with the group of surgical survivors (see Table 3). Even if not all differences achieved statistical significance due to the relative small sample size, the medical non-survivors overall appeared to represent a sicker subcohort from the beginning with a longer pre-CDC length of stay and more comorbidities; in addition, however, they also displayed decreased clinical signs, hence suggesting a masking of the disease severity, or the patients were in a condition where the clinical exam was less reliable (e.g., on the respirator).

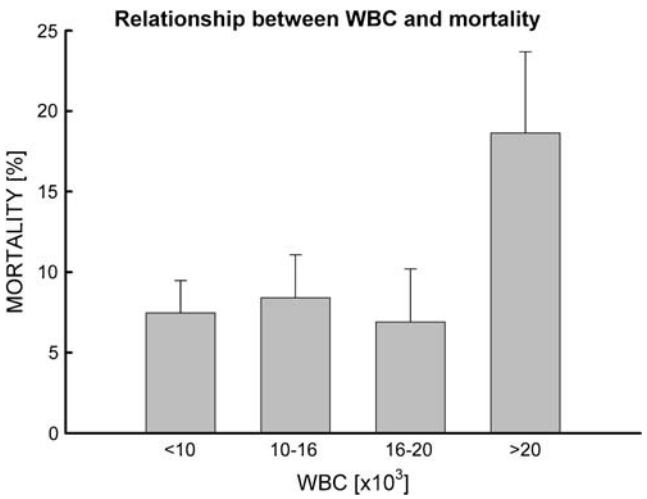

Figure 1 Correlation between WBC and mortality.

Comparison of CDC in Surgical/Fatal Group vs. Medical Survivors Group

A similar analysis was carried out by comparing patients with recognized severe disease, i.e., patients with *surgical/fatal* CDC on one hand with patients who survived with medical management on the other hand. As shown in Table 4, there were statistically significant differences between the two groups, which involved both preexisting parameters, scores, and elements of the clinical presentation. Yet, one also has to acknowledge that the medical survivor group contained 68 patients with an ASA of 4, and even two patients with an initial ASA of 5, which they paradoxically survived.

Medical vs. Surgical Management Group

Last but not least, we analyzed the impact of the various parameters on the probability to undergo surgery. The combination of metronidazole + vancomycin was used more frequently in the surgical group (p<0.05). Furthermore, pre-illness pulmonary disease and respiratory failure at time of CDC were significantly associated with a need for surgery. In addition, the following factors showed statistical significance (as shown in Table 5a): temperature, heart rate, WBC, abdominal pain, tenderness, and distention, and the APACHE II score., whereas differences among other factors did not achieve statistical significance (Table 5).

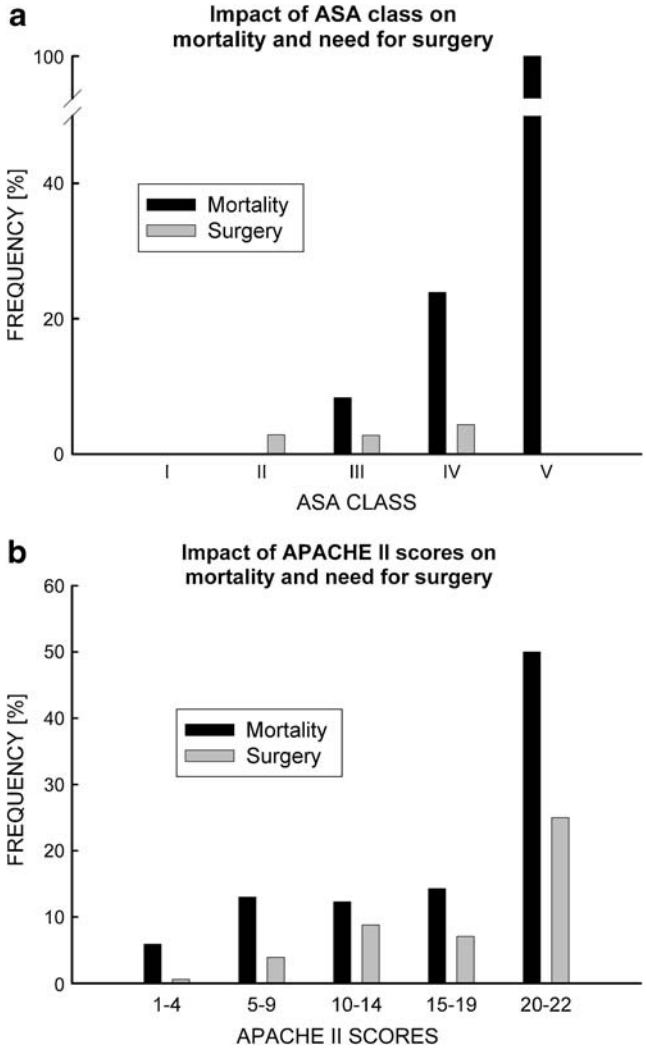

Figure 2 **a** Impact of ASA class on mortality and the needed surgery. **b** Impact of APACHE II class on mortality and the needed surgery.

Discussion

Fulminant colitis has been reported to develop in 3–8% of patients with *C. difficile* infection,[14] but in our cohort, it occurred in roughly 12.6% of all patients. Predictors of fatal outcome continue to be unsatisfactorily delineated. Recent surgical publications have focused on subsets of patients who underwent colectomy for fulminant pseudomembranous colitis.[7,12,15–18] Invariably, these surgical series with a median of 37 reported patients (range 14–130) demonstrated a high mortality rate of 34–47%. However, given that even more extensive colorectal resections such as a proctocolectomy are safely performed with minimal overall mortality of 2.3% (0.7–5.4%) in the elective and emergency context of ulcerative colitis,[13] one has to speculate that not the procedure per se is responsible for the poor outcome but that the surgical intervention for the reported CDC patients simply came too late. This view is shared by other authors who, based on their series, suggested that operative intervention for fulminant *C. difficile* colitis earlier in the course and prior to multi organ failure was associated with decreased mortality.[7,16]

Key to implementing such a strategy to the clinical management is to identify parameters that predict unfavorable outcomes before the point of no return has been crossed. Some authors reported factors such as mental status changes, length of medical treatment, and hemodynamic instability with vasopressor requirement to correlate with poor outcome.[12,17,19] A recent critical care review on CDC equally concluded that emergent colectomy prior to vasopressor therapy was beneficial in preventing patient death.[14] Other authors, analyzing CDC in the critical care setting in 165 patients, suggested that operative intervention provided little benefit to patients with WBC less than 20,000 and normal lactate levels.[15] However, a closer look at those data with 38 surgical and 127 non-surgical patients provided inadequate power (only two patients) to substantiate the stated conclusion and revealed an even higher mortality rate in non-operated patients (41–95%),[15] hence rather suggesting an invariably unfavorable outcome if any critical care treatment is needed.

Nonetheless, the clinical paradigm that "sicker patients do worse" has not been uniformly confirmed either. Immunosuppression after kidney or pancreas–kidney transplantation in 702 patients, for example, was neither associated with a higher incidence of CDC overall (5.5%) nor of fulminant colitis with a need for a colectomy in particular (5.7%, 2/35 patients).[20] Similarly, Gellad et al. showed no significant difference between the development of complicated CDC between notably more morbid solid organ transplanted patients as compared to a non-transplanted reference groups.[21]

Our own study was undertaken to further investigate the issue. Even though it is not the largest series with regards to the reported colectomy patients, it is unique in the sense that we eliminated the selection bias of surgery- or fulminant-only populations by including and analyzing all inpatients of a well-defined single tertiary institution in order to look at clinical parameters and outcomes. It was our goal to analyze a large number of parameters in an attempt to define host constellations, which would lead to the development of the more aggressive form of this disease and hence justify an early or earlier surgical intervention. Our data were able to identify a number of host factors, which were significantly associated with a poorer outcome when we compared our survival group versus the non-survivors. An increased mortality on one hand was associated with the patients' preexisting conditions (e.g., renal and pulmonary insufficiency, a higher ASA class, and use of steroids). On the other hand, specific clinical

Table 3 Comparison of Medical Non-survivors to Surgical Survivors

Factors	Parameter	Surgical survivors (n=9)	Medical non-survivors (n=36)	p value
Preexisting	Pre-CDC LOS [days]	5.2	15.6	0.055
	Renal insufficiency [%]	0	36	0.098
	Diabetes [%]	0	47	0.031[a]
	Hypertension [%]	11	47	0.255
	Steroid use [%]	11	42	0.163
Scores	ASA [median]	3	4	0.018[a]
	APACHE II	8.1	7.1	0.187
Presentation	Abdominal pain [%]	78	28	0.022[a]
	Tenderness [%]	89	19	0.001[a]
	Abdominal distention [%]	67	22	0.075
	Acute abdomen [%]	56	0	0.010[a]
	Normal abdominal exam [%]	22	58	0.099
	Mental status change [%]	0	11	0.617
	Sepsis [%]	22	19	0.909
	Organ dysfunction [%]	33	69	0.099
	Renal failure [%]	22	44	0.312
	Respiratory failure [%]	33	42	0.711
	WBC	19.0	15.5	0.055

[a] Statistically significant difference

findings, e.g., a lower diastolic blood pressure, a higher APACHE II score, evidence of toxic megacolon, higher WBCs, and clinical signs of sepsis and organ dysfunction (renal, pulmonary, and cerebral), were negative predictors. As shown by others,[15] we found that the WBCs above 20,000 were associated with a higher mortality rate, even if there was not strictly a linear correlation.

The pre-CDC length of hospital stay was repeatedly found to have an impact on survival. The reasons for this observation are not clearly apparent. However, these patients were often more seriously ill from other causes, and furthermore, one might also speculate that the CDC might have smoldered for a longer period under the radar screen. This interpretation is supported by the data that show a masking of clinical parameters in the medical non-survivors. This important finding emphasizes the need to be on high alert in patients with the mentioned preexisting conditions and who are inadequately assessable, e.g., because they show neurological impairment, sedation, or are otherwise intensive care dependent as demonstrated by higher ASA and APACHE II scores. It is of note that the mortality among our mid-classification of APACHE II (5–19) scores was

Table 4 Comparison of Medical Survivors to Surgical and/or Fatal CDC

Factors	Parameter	Medical survivors (n=348)	Surgical or fatal CDC (n=50)	p value
Preexisting	Pre-CDC LOS [days]	10.7	13.6	0.021
	Renal insufficiency [%]	18.4	30.0	<0.001
	Steroid use [%]	21.3	36.0	<0.001
Scores	ASA [median]	3	3	<0.001
	APACHE II	6.0	8.1	0.005
Presentation	Acute abdomen [%]	1.1	10.0	<0.001
	Normal abdominal exam [%]	60.3	46.0	<0.001
	Mental status change [%]	3.7	8.0	<0.001
	Sepsis [%]	1.7	18.0	<0.001
	Organ dysfunction [%]	22.1	62.0	<0.001
	renal failure [%]	15.8	40.0	<0.001
	respiratory failure [%]	4.3	38.0	<0.001
	WBC	12.3	16.7	0.008

Table 5 Comparison of Surgical and Non-surgical Patients

Factors	Parameter	Non-surgical (n=384)	Surgical (n=14)	p value
Preexisting	Pre-CDC LOS [days]	11.8	8.1	0.810
	Age	59.5	60.2	0.878
	Cancer [%]	28.6	21.4	0.779
	Renal insufficiency [%]	20.1	14.3	0.849
	Diabetes [%]	33.3	7.14	0.077
	HTN [%]	47.6	35.7	0.514
	CAD [%]	21.9	28.6	0.791
	Steroid [%]	23.2	21.4	0.865
	Chemotherapy [%]	10.9	0	0.387
Presentation	Abdominal pain [%]	38.3	78.6	0.006
	Abdominal tenderness [%]	27.6	85.7	<0.001
	Abdominal distention [%]	26.8	71.4	<0.001
	WBC	12.7	19.8	0.014
	HR	91.6	111.1	0.003
	Temperature	99.1	100.3	0.010
	Respiratory rate	20.2	23.1	0.004
	Respiratory failure [%]	7.8	28.6	0.025
	Hematocrit	32.2	33.7	0.591
	Albumin	2.82	2.58	0.176
	Systolic BP [mmHg]	124.7	119.9	0.712
	Diastolic BP [mmHg]	68.2	67	0.871
	Nausea [%]	18.7	42.8	0.059
	Vomiting [%]	8.67	14.3	0.796
	Organ failure [%]	26.6	42.9	0.298
	Mental status change	3.7	0	0.895
	CNS failure [%]	3.7	0	0.895
	Hepatic failure [%]	3.6	0	0.599
Scores	APACHE II	6.1	10.6	<0.001
	ASA [median]	3	3	0.954

similar, and the mortality did not seem to correlate with increasing scores in this segment. In addition, we found the mortality rate in that APACHE range to be 14.3%, which is markedly less than the 25% originally reported when the APACHE scoring system was introduced.[22]

The mortality rates for our surgical subgroup were in the same range as reported by other authors.[7,12,15–18] This known fact and the new finding of a much larger group of non-survivors who were not even operated suggests that a distinct set of disadvantages might have prevented these individuals from getting timely access to surgery.

In summary, we identified a number of parameters that are associated with unfavorable outcome. Yet we continue to have a limited understanding when it comes to a subgroup of medically managed patients who survived despite seemingly poor prognostic indicators. While our data are encouraging, they should for now be interpreted with clinical caution when it comes to the actual recommendation to treat an individual patient more aggressively. We suggest to use these risk factors to sensitize clinicians to the need of carefully assessing these complex patients with the constant question in mind whether a more aggressive treatment, e.g., a life-saving operation, should be considered.

Conclusion

With independent impact from both host factors and the bacterial virulence, the pathophysiology leading to an unfavorable course and outcome of *C. difficile* colitis remains a challenge. Our study not only identified several clinical factors, which were associated with increased mortality from CDC, but more importantly pointed out a subset of sicker patients, who due to blunting of clinical signs and symptoms carries a higher risk of poor outcome. Future investigations should be designed in a prospective fashion using our current criteria to monitor the continuous disease progression and narrow down the actual "point of no return" in order to minimize potentially preventable fatalities.

References

1. Kaiser AM. McGraw-Hill's Manual of Colorectal Surgery. 1st ed. New York: McGraw-Hill, 2008.
2. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis 2008;46(Suppl 1): S12–18.
3. Mitty RD, LaMont JT. Clostridium difficile diarrhea: pathogenesis, epidemiology, and treatment. Gastroenterologist 1994;2(1):61–69.
4. Shen EP, Surawicz CM. The changing face of Clostridium difficile: what treatment options remain? Am J Gastroenterol 2007;102(12):2789–2792.
5. Gerding DN, Muto CA, Owens RC Jr. Treatment of Clostridium difficile infection. Clin Infect Dis 2008;46(Suppl 1):S32–42.
6. Ricciardi R, Rothenberger DA, Madoff RD, Baxter NN. Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. Arch Surg 2007;142(7):624–631. discussion 31.
7. Koss K, Clark MA, Sanders DS, Morton D, Keighley MR, Goh J. The outcome of surgery in fulminant Clostridium difficile colitis. Colorectal Dis 2006;8(2):149–154.
8. McFarland LV. Update on the changing epidemiology of Clostridium difficile-associated disease. Nature Clinical Practice Gastroenterology & Hepatology 2008;5(1):40–48.
9. Loo VG, Poirier L, Miller MA et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353(23):2442–2449.
10. Hermsen JL, Dobrescu C, Kudsk KA. Clostridium difficile infection: a surgical disease in evolution. J Gastrointest Surg 2008;12(9):1512–1517.
11. Pepin J, Valiquette L, Gagnon S, Routhier S, Brazeau I. Outcomes of Clostridium difficile-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. Am J Gastroenterol 2007;102(12):2781–2788.
12. 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(2):150–154. discussion 5.
13. Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterology 2008;134(3):680–687.
14. Adams SD, Mercer DW. Fulminant Clostridium difficile colitis. Curr Opin Crit Care 2007;13(4):450–455.
15. Lamontagne F, Labbe AC, Haeck O et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg 2007;245(2):267–272.
16. Ali SO, Welch JP, Dring RJ. Early surgical intervention for fulminant pseudomembranous colitis. Am Surg 2008;74(1):20–26.
17. Hall JF, Berger D. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. Am J Surg 2008;196 (3):384–388.
18. Pepin J, Truc Vo T, Boutros M et al. Risk factors for mortality following emergency colectomy for fulminant Clostridium difficile infection. Dis Colon Rectum 2009;52(3):400–405.
19. Kyne L, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. Age & Ageing 1999;28(2):107–113.
20. Keven K, Basu A, Re L et al. Clostridium difficile colitis in patients after kidney and pancreas–kidney transplantation. Transpl Infect Dis 2004;6(1):10–14.
21. Gellad ZF, Alexander BD, Liu JK et al. Severity of Clostridium difficile-associated diarrhea in solid organ transplant patients. Transpl Infect Dis 2007;9(4):276–280.
22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13 (10):818–829.