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Laboratory markers predictive of fulminant *Clostridioides difficile* infection refractory to fluid resuscitation

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SUMMARY

Background: Old age, leucocytosis, hypoalbuminemia, and elevated creatinine have been identified as risk factors for fulminant *Clostridioides difficile* infection (CDI). High ATLAS scores have also been linked to fatal disease. The affiliated studies, however, involved patients prescribed metronidazole - a regimen no longer standard of care. The variables were thus reassessed in patients prescribed optimal therapy.

Methods: Adults hospitalized with CDI at University of Kentucky Medical Center were retrospectively reviewed. Enrolled subjects were separated according to disease classification i.e. non-severe/severe versus fulminant CDI. Fulminant patients were further subdivided into hypotensive persons responsive to fluid resuscitation, and those with sequent shock, ileus, or megacolon. Following partition, the cohorts underwent correlation analysis.

Findings: Forty-five subjects had non-severe/severe disease. Thirteen fulminant CDI patients responded to fluid resuscitation. Seventeen fulminant CDI patients developed shock, ileus, or megacolon. Median WBC counts, albumin values, and ATLAS scores varied among the cohorts. Although WBC counts were similar among the fulminant subsets, declining albumin values and increasing ATLAS scores mirrored disease worsening. Logistic regression revealed albumin values < 20 g/L (odds ratio [OR] 3.91) and ATLAS scores ≥ 6 (OR 5.03) to predict critical illness in hypotensive persons.

Conclusion: Median WBC counts, albumin values, and ATLAS scores differed in patients separated by CDI severity. A notable variance in albumin values and ATLAS scores between fluid responsive fulminant disease and critical illness was moreover seen. The finding suggests hypoalbuminemia and high ATLAS scores in hypotensive CDI patients may herald shock, ileus, or megacolon.

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Introduction

Clostridioides difficile is the leading infectious cause of healthcare-associated diarrhea [1]. Risk factors for *C. difficile* infection (CDI) include advanced age, prolonged hospitalization, and severe underlying illness [2]. The most widely recognized modifiable risk factor, though, is antibiotic use. The risk of disease increases up to 10-fold during antibiotic therapy and CDI accounts for 15 to 25% of all episodes of antibiotic-associated colitis [3,4].

Following fecal-oral transmission of *C. difficile*, some patients become asymptomatic carriers of the organism. Others incur a variety of CDI-related manifestations. Watery diarrhea and abdominal pain predominate in uncomplicated cases [5]. Progressive disease, however, can lead to fulminant CDI — characterized by hypotension, shock, ileus, or toxic megacolon. Life-saving colectomy is oftentimes needed in the latter scenario [1].

Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) criteria for disease severity has long been defined by serum white blood cell counts and creatinine levels. Previous IDSA/SHEA clinical practice guidelines employed the classification to guide treatment. Initial episodes of mild-to-moderate uncomplicated CDI called for metronidazole while severe disease necessitated oral vancomycin [6]. Several studies have since shown vancomycin to be superior in cure and disease recurrence [7—10]. As a result, present guidelines no longer support metronidazole monotherapy. Vancomycin or fidaxomicin is now considered the drug of choice for uncomplicated CDI regardless of severity [1].

The standard antibiotic regimen for fulminant CDI continues to be oral vancomycin plus intravenous metronidazole [1]. Even with optimal therapy, though, fulminant CDI can prove fatal. Mortality rates of 34—80% have been reported in patients with fulminant disease [11]. Prior studies have found old age, leucocytosis, hypoalbuminemia, and elevated creatinine to be risk factors for fulminant CDI [12—15]. A study by Hernández-García *et al.* involving 102 CDI patients additionally revealed a 100% mortality rate in the 4 persons whose ATLAS score was ≥ 8 [16]. However, several patients in the respective studies were administered metronidazole alone. The variables were thus reassessed in subjects prescribed contemporary therapy.

Methods

Study design and subject selection

Adult patients hospitalized with an initial episode of CDI between 1st January 2018 and 30th June 2020 at University of Kentucky Medical Center (UKMC) were identified. Those with uncomplicated disease who received either oral vancomycin or fidaxomicin, and fulminant CDI patients administered oral vancomycin plus intravenous metronidazole underwent further analysis. Persons with a history of recurrent CDI, irritable bowel syndrome, inflammatory bowel disease, prior colonic surgery, or chronic diarrhea were excluded. Those administered laxatives 3 days prior to the onset of attributable CDI symptoms, discharged against medical advice prior to completion of therapy, or had care withdrawn prematurely were also excluded. No patients received fecal microbiota transplantation, bezlotoxumab, rifaximin, or tigecycline.

Participants were divided into three groups. One group contained non-severe/severe CDI patients. Fulminant CDI patients constituted the other two groups and were separated according to treatment needs. Hypotensive patients responsive to fluid resuscitation constituted one subset. Hypotensive patients who later developed shock, ileus, or megacolon comprised the other subset.

Age, sex, comorbid conditions, inpatient medications, and imaging results of subjects were recorded. White blood cell counts, serum creatinine levels the day of CDI diagnosis (or within one day of diagnosis if not available), and lattermost obtained albumin values in the 5 days preceding CDI diagnosis (or the day after if not available) were documented. Finally, vital signs and pertinent patient signs/symptoms as per electronic medical record (EMR) documentation were noted.

Clinical data collection and definitions

Hemodynamically stable patients with unexplained acute diarrhea ($\geq$3 unformed stools over 24 hours) plus positive stool *C. difficile* nucleic acid amplification test (NAAT) and toxin enzyme immunoassay (EIA) results were diagnosed with uncomplicated CDI. Those with a white blood cell count $<$ 15 x 10^9 cells/litre and a serum creatinine level $<$ 133 umol/L were labelled as non-severe. Persons with a white blood cell count $\geq$ 15 x 10^9 cells/litre or a serum creatinine level $\geq$ 133 umol/L were designated as severe.

Patients with positive *C. difficile* NAAT and toxin EIA results who were hypotensive or suffering from shock, ileus, or megacolon were diagnosed with fulminant CDI. Hypotension was defined as a systolic blood pressure $<$ 100 mm Hg or a mean arterial pressure $<$ 70 mm Hg while experiencing CDI-related symptoms. Shock was defined as hypotension requiring vasopressor agents. Instances of ileus and megacolon were diagnosed in persons with compatible clinical manifestations and supportive radiographic or computed tomography imaging findings. Patient deaths were accounted for if attributable to CDI.

Charlson comorbidity index (CCI) and ATLAS score values were calculated using conventional scoring methods [17,18]. Relevant medical conditions detailed in EMR documentation determined patient CCI values. ATLAS scores incorporated patient laboratory data according to timeline stipulations detailed previously.

Treatment regimens

Oral vancomycin 125 mg 4 times daily or fidaxomicin 200 mg twice daily was administered to patients with non-severe/severe CDI. Those with fulminant disease received vancomycin 500 mg 4 times daily either orally or by nasogastric tube plus parenteral metronidazole 500 mg every 8 hours.

Statistical analysis

Data were analyzed using SAS version 9.4 (Cary, NC, USA). *P*-values $<$ 0.05 were considered significant. Descriptive statistics were conducted to describe the sample data with means, standard deviations, medians, and interquartile ranges for all continuous variable, plus frequencies and percentages for all categorical variables. To examine relationships between the study variables and the outcome, analysis of variance was

conducted for continuous variables, and chi-square tests were conducted for categorical variables. Due to sample size, the two complicated groups were grouped together to create a dichotomous outcome. Logistic regression was conducted to obtain unadjusted and adjusted odds ratios. The adjusted model only included variables that were significant at the 0.05 level.

Results

One hundred eighty-two CDI patients were identified during the study period. Implementing exclusion criteria resulted in a study population of 75 subjects. Forty-five patients were uncomplicated, with 22 persons suffering from severe disease. Thirty subjects had fulminant CDI. Thirteen patients responded to fluid resuscitation. Seven persons suffered shock, 3 were diagnosed with ileus, and 7 patients had megacolon. Four patients with megacolon underwent colectomy (Figure 1).

A slight mean age difference was seen among the cohorts. The disparity was not statistically significant, however. Elevated median creatinine levels were seen in all subsets. While a mild worsening of renal function paralleled disease progression, the variance was not statistically significant. Of note, 4 persons with non-severe/severe CDI and 2 persons with fulminant CDI had dialysis-dependent chronic kidney disease at the time of hospitalization. Their serum creatinine levels were not incorporated into median computations. The median WBC count of the non-severe/severe CDI group was within normal

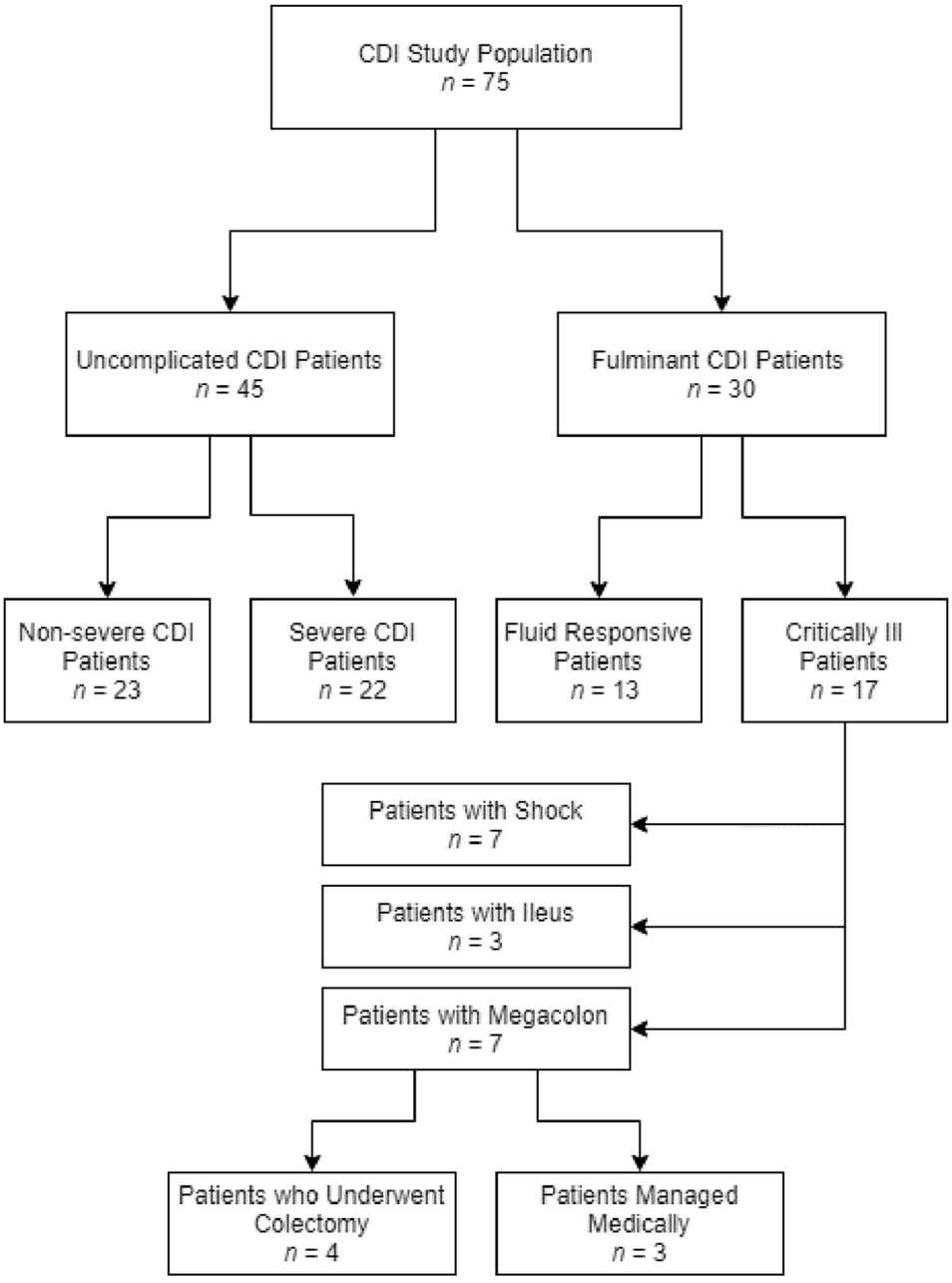

Figure 1. Patient distribution.

limits at 7.39 x 10^9 cells/litre. Both fulminant CDI subsets exhibited elevated median WBC counts: 14 x 10^9 cells/litre in patients responsive to fluid resuscitation and 14.9 x 10^9 cells/litre in patients with shock, ileus, or megacolon. A stepwise decline in albumin and increase in ATLAS score coincided with disease progression. The finding was especially noteworthy in fulminant CDI patients. Median albumin values fell from 24 g/L in subjects with fluid responsive disease to 18 g/L in those with shock, ileus, or megacolon. Median ATLAS scores rose from 5 in persons with fluid responsive disease to 6 in those with shock, ileus, or megacolon (Table I). Logistic regression revealed the two variables to correlate with the development of critical illness in hypotensive CDI patients. Specifically, albumin values $<$ 20 g/L (odds ratio [OR] 3.91; 95% confidence interval [CI] = 1.11−13.81) and ATLAS scores $\geq$ 6 (OR 5.03; 95% CI = 1.58−16.01) predicted ensuing shock, ileus, or megacolon after covariate adjustment (Table II).

The possibility of pre-existing comorbidities impacting disease severity led us to compare median CCI values of the cohorts. The decision was additionally influenced by Baiomi *et al*. associating high CCI scores with CDI-related mortality [19]. No statistically significant difference was seen.

CDI culminated in 7 deaths. All had fulminant disease with accompanying shock, ileus, or megacolon. Only one of the patients who expired had an ATLAS score $\geq$ 8. Furthermore, two survivors (one belonging to the non-severe/severe group and the other belonging to the fluid responsive fulminant CDI group) had ATLAS scores $\geq$ 8.

Discussion

Fulminant CDI is a substantial cause of patient morbidity and mortality. Early diagnosis is crucial in disease management and minimizing poor outcomes [20]. Antibiotics along with aggressive fluid resuscitation, electrolyte replacement, and nutritional support are essential in hypotensive patients [21]. Even with these measures, however, shock, ileus, or megacolon can abruptly occur.

The potential for CDI patients to rapidly deteriorate underscores the need for reliable prognostic markers. As mentioned before, while several risk factors for fulminant CDI have been identified, they were validated in subjects prescribed substandard therapy. Upon reassessing the variables, we found leucocytosis and hypoalbuminemia to correlate with fulminant CDI. While ATLAS scores $\geq$ 8 were not inevitably fatal, higher scores were associated with fulminant CDI as well. Of more clinical importance was the relationship between the latter two variables and spectrum of disease. Median WBC counts doubled in subjects with fulminant CDI compared to those with non-severe/severe disease. That said, no sizeable difference was seen between the fulminant CDI subsets. On the other hand, declining albumin values and increasing median ATLAS scores mirrored disease worsening. The finding may help better manage hypotensive CDI moving forward.

Speaking further, our study suggests that marked hypoalbuminemia and elevated ATLAS scores in hypotensive CDI patients may portend shock, ileus, or megacolon. Early mitigation efforts in CDI patients with shock, ileus, or megacolon has been associated with improved outcomes [20]. Identifying those at risk for critical illness and implementing precautionary measures such as empiric intensive care unit (ICU) admission, a lowered threshold for colectomy, and a greater willingness to pursue fecal microbiota transplantation could prove beneficial. Appreciating moderately elevated ATLAS scores in hypotensive CDI patients may also better guide patient care. Receipt of unrelated antimicrobials during CDI therapy is one component of the ATLAS scoring system. Not uncommonly, broad-spectrum empiric antibiotics are given to hypotensive CDI patients over concerns of concomitant occult bacterial infection(s). Given our findings, this may be worth reconsidering in persons with already elevated ATLAS scores so to not further the risk of shock, ileus, or megacolon.

While regression analysis found albumin values $<$ 20 g/L and ATLAS scores $\geq$ 6 to herald future shock, ileus, or megacolon, the study population was modest - resulting in a relatively wide confidence interval. This cautions against designating the figures as formal cutoffs. Two constraints were largely responsible for paring our census. First, the 2018 relegation of metronidazole monotherapy by IDSA/SHEA clinical practice

Table II
Odds ratios for predictors of fulminant CDI refractory to fluid resuscitation

Variable	OR (95% CI)	aOR (95% CI)
Age	0.99 (0.96−1.02)	—
WBC	1.08 (1.02−1.14)	—
Creatinine	1.22 (0.83−1.80)	—
Albumin $<$ 20 g/L	4.63 (1.41−15.22)	3.91 (1.11−13.81)
ATLAS score $\geq$ 6	5.69 (1.86−17.42)	5.03 (1.58−16.01)
CCI score	1.09 (0.89−1.33)	—

Abbreviations: aOR, adjusted odds ratio; CCI, Charlson comorbidity index; CI, confidence interval; WBC, white blood cell.

Table I
Patient characteristics

Variable	All patients (n = 75)	Non-severe/ Severe (n = 55)	Hypotensive (n = 13)	Critically Ill (n = 17)	*P*-value
Age (years), mean (SD)	59.0 (15.7)	60.0 (14.7)	59.8 (14.5)	55.7 (19.2)	0.61
WBC (x 10^9 cells/litre), median (IQR)	10.0 (11.2)	7.4 (9.1)	14.0 (11.0)	14.9 (25.0)	0.04
Cr (umol/L), median (IQR)	114 (97)	106 (88)	124 (133)	133 (106)	0.63
Albumin (g/L), median (IQR)	25 (9)	26 (8)	24 (4)	18 (5)	$<$0.0001
ATLAS score, median (IQR)	5 (3)	4 (3)	5 (3)	6 (1)	$<$0.0001
CCI score, median (IQR)	4 (4)	4 (4)	5 (3)	4 (3)	0.69

Abbreviations: CCI, Charlson comorbidity index; Cr, creatinine; IQR, interquartile range; SD, standard deviation; WBC, white blood cell.

guidelines narrowed the recruitment interval. Second, the CDI diagnostic testing method at UKMC changed from NAAT alone to multistep NAAT plus toxin in January 2018. Only patients who underwent multistep testing were enrolled to avoid incorporating false positives. The decision strengthened internal validity in exchange for reduced demographics. The recruitment interval was further narrowed and suspected non-diagnosed CDI patients (false negatives secondary to toxin EIA's limited sensitivity) were eliminated from consideration.

Additional limitations deserve mention. Characteristic CDI symptoms were not personally confirmed in subjects given the study's retrospective nature. *C. difficile* colonized patients may have unknowingly participated as a result. Targeted measures were implemented to avoid this possibility, however. Disease specific signs/symptoms i.e. acute diarrhea, ileus, megacolon were verified in all patients via EMR review, and exclusion criteria eliminated common alternative causes e.g. laxative use, inflammatory bowel disease, prior colonic surgery, etc. This aside, no subjects underwent NAP1/BI/027 molecular typing. Said testing is not routinely performed at UKMC - reserved instead for epidemiological purposes. No outbreaks occurred during the study period to warrant strain typing. It is thus unclear if NAP1/BI/027 impacted our findings.

Conclusion

WBC counts, albumin values, and ATLAS scores differed in CDI patients separated by severity. More importantly, declining albumin values and increasing ATLAS scores mirrored disease progression. Albumin values < 20 g/L and ATLAS scores ≥ 6 predicted ensuing shock, ileus, or megacolon in hypotensive persons. While validated by regression analysis, our small study population cautions against firmly utilizing these thresholds for risk stratification. Future large-scale studies to explicitly define inauspicious hypoalbuminemia, ATLAS scores are encouraged.

Credit

Omar Ahmad: Conceptualization, Methodology, Investigation, Data Curation, Writing — Original Draft, Writing — Review & Editing.

Timothy Crawford: Validation, Formal Analysis, Writing — Original Draft.

Vaneet Arora: Software, Resources, Data Curation.

Mitu Maskey: Conceptualization, Supervision.

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Declarations of Interest

None.

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