Clostridium Difficile-Associated Infection in Trauma Patients: Development of the *Clostridium Difficile* Influencing Factors (CDIF) Score

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ABSTRACT

Context: *Clostridium difficile*-associated infection (CDAI) can result in longer hospitalization, increased morbidity, and higher mortality rates for surgical patients. The impact on trauma patients is unknown, however.

Objective: To assess the effect of CDAI on trauma patients and develop a scoring system to predict CDAI in that population.

Methods: Records of all trauma patients admitted to a Level I Trauma Center from 2001 to 2014 were retrospectively reviewed. Presence of CDAI was defined as evidence of positive toxin or polymerase chain reaction. Patients with CDAI were matched to patients without CDAI using propensity score matching on a ratio of 1:3.

Main Outcome Measures: Primary outcome was inhospital mortality. Secondary outcomes included length of stay and need for mechanical ventilation. A decision-tree analysis was performed to develop a predicting model for CDAI in the study population.

Results: During the study period, 11,016 patients were identified. Of these, 50 patients with CDAI were matched to 150 patients without CDAI. There were no differences in admission characteristics and demographics. Patients in whom CDAI developed had significantly higher mortality (12% vs 4%, $p < 0.01$), need for mechanical ventilation (57% vs 23%, $p < 0.01$), and mean hospital length of stay (15.3 [standard deviation 1.4]) days vs 2.1 [0.6] days, $p < 0.0$).

Conclusion: In trauma patients, CDAI results in significant morbidity and mortality. The *C difficile* influencing factor score is a useful tool in identifying patients at increased risk of CDAI.

INTRODUCTION

Since Trunkey et al[1] in 1983 first described the trimodal distribution of deaths for trauma patients, there has been major improvement in the management of critically injured patients. After the widespread implementation of trauma centers, several studies have demonstrated that the third peak of late deaths has diminished. However, despite those changes, there is still a high incidence of morbidity and mortality for patients who remain critically ill in the surgical intensive care unit (ICU) for more than 7 days. *Clostridium difficile*-associated infection (CDAI) is a modifiable factor that can result in significant morbidity and has a higher prevalence in critically ill patients. Several recent studies have implemented severity assessment scores for hospitalized patients.[2-4] Although there is a plethora of studies about the impact of CDAI in the medical patient, there is a paucity of data for the trauma patient population. There currently exists no known predictive model or scoring system that can accurately predict the risk of *C difficile* infection in trauma patients using patients' admission characteristics.

The present study hypothesized that the development of CDAI in the setting of a traumatic injury results in significantly higher morbidity and mortality, and we set out to develop a scoring system that would predict the probability of CDAI development after a traumatic injury.

METHODS

Patients and Setting

After institutional review board approval, the medical records from all patients admitted to an urban Level I Trauma Center from 2001 to 2014 were retrospectively reviewed from the prospectively maintained hospital trauma database. Patients in whom CDAI developed during the index hospitalization were identified. Verification of CDAI was based on either a positive assay for *C difficile* toxin or polymerase chain reaction result. The decision to assess for CDAI was physician driven. Patients were excluded if they were younger than age 18 years or pregnant. The following variables were extracted: Age, race, sex, mechanism of injury, admission physiologic parameters, injury severity indexes, and admission service.

The study population was divided into 2 groups on the basis of CDAI development. Patients in whom CDAI developed during the index hospitalization were matched to patients who did not contract the infection, using propensity score matching on a ratio of 1:3 to ensure homogeneity between the 2 groups. After propensity score matching, a chart review was performed to identify the specific patterns of injury, type of antibiotic given during the hospitalization, and white blood cell count (WBC) at admission.

The primary outcome was inhospital mortality. Secondary outcomes included the need for ventilator support, ICU

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length of stay, total number of ventilator days, and hospital length of stay.

Statistical Analysis

The cohorts with and without CDAI were compared for differences in demographics and clinical characteristics using univariate analysis. Chi squared or Fisher exact tests were used to compare the proportions. Continuous variables were examined for normality of distribution using the Shapiro-Wilks test. Student *t*-test was used for normally distributed continuous variables, whereas the Mann-Whitney U test was used for nonnormally distributed variables.

Propensity score matching was used to minimize the variability of the study outcomes. Propensity score was generated using a binary logistic regression. Included in the regression model were all demographic and clinical baseline characteristics that differed between the 2 groups at $p < 0.05$. Each patient was matched with controls in a 1:3 ratio within a narrow caliper (0.003) of propensity, without replacement. The caliper was equal to one-fourth of the standard deviation of the generated propensity scores. After propensity score matching, the McNemar χ^2 test was used to compare proportions, and the Wilcoxon signed rank test was used to compare means, to ensure the suitability and applicability of the process.

Further univariate analyses were performed to identify differences between the groups. A stepwise logistic regression was then performed using variables that were different at $p < 0.2$. The dependent variable was development of CDAI. A simplified clinical risk assessment tool was derived by assigning point values to the ratios of the β coefficients. A composite risk score, the *C difficile* influencing factor (CDIF) score, was subsequently defined as the summation of these point values. The C statistic of the model was subsequently calculated to assess whether discriminative capacity was preserved.

To assess the validity of the model, we used a distinct cohort of patients from a different period. The CDIF score was calculated for each patient, and a multivariate logistic regression was performed using the development of *C difficile* infection as the outcome. Adjusted odds ratios with 95% confidence intervals were derived from the regression. The C statistic of the model was calculated to assess the validity of the model and whether discriminative capacity was preserved.

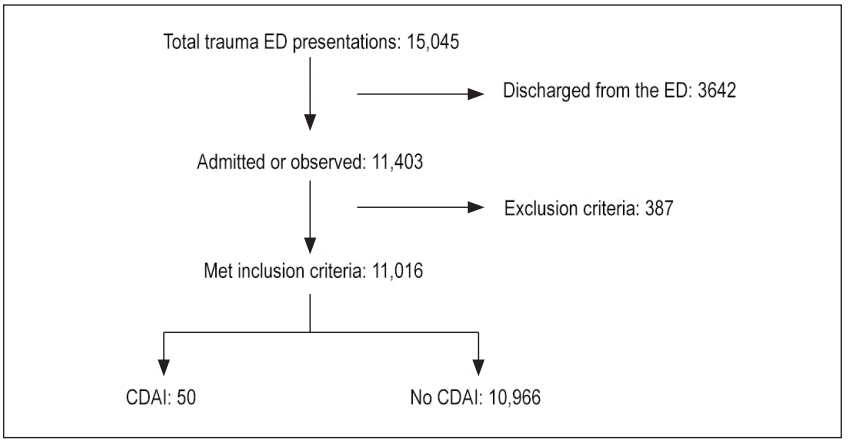

Figure 1. CONSORT diagram of study population.

CDAI = *Clostridium difficile*-associated infection; ED = Emergency Department.

RESULTS

During the study period, a total of 11,016 patients were identified (Figure 1). Of those, only 0.45% (50) had a diagnosis of CDAI. After propensity score matching, 50 patients with CDAI were matched to 150 patients without CDAI in a ratio of 1:3 (Table 1). The mean age of the study population was 32 years. The majority (68%) were men and African American (58%). Penetrating mechanism of injury accounted for 30% of the cases.

Table 1. Demographics and admission characteristics of study population

Variables	Overall (N = 200)	*Clostridium difficile* positive (n = 50)	*Clostridium difficile* negative (n = 150)	p value	Validation cohort (n = 875)
Age, years, mean (SD)	32 (11)	35 (13)	32 (9)	0.31	34 (5)
Men, no. (%)	136 (68.0)	33 (66.0)	103 (68.7)	0.73	551 (63.0)
Race, no. (%)					
African American	115 (57.5)	27 (54.0)	88 (58.7)	0.17	417 (47.7)
White	79 (39.5)	18 (36.0)	61 (40.7)		366 (41.8)
Admission physiologic values					
SBP, mmHg, mean (SD)	151 (36)	151 (39)	152 (32)	0.79	147 (30)
HR/min, mean (SD)	92 (23)	95 (28)	91 (22)	0.24	89 (19)
RR/min, mean (SD)	18 (5)	19 (6)	18 (5)	0.44	19 (4)
GCS, median (range)	13 (3-15)	13 (3-15)	13 (3-15)	0.6	
Injury severity indexes, no. (%)					
Head AIS < 3	79 (39.5)	20 (40.0)	59 (39.3)	0.15	144 (16.5)
Chest AIS < 3	83 (41.5)	19 (38.0)	64 (42.7)	0.11	109 (12.5)
Abdominal AIS < 3	52 (26.0)	16 (32.0)	36 (24.0)	0.09	45 (5.1)
Penetrating mechanism of injury	59 (29.5)	13 (26.0)	46 (30.7)	0.53	97 (11.1)
Admission service, no. (%)					
Trauma	163 (81.5)	37 (74.0)	126 (84.0)	0.1	524 (59.9)
Orthopedics	13 (6.5)	2 (4.0)	11 (7.3)		160 (18.3)
Neurosurgery	24 (12.0)	11 (22.0)	13 (8.6)		40 (4.6)

AIS = Abbreviated Injury Scale; GCS = Glasgow Coma Scale; HR = heart rate; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation.

A total of 80 patients had a severe head injury defined by the Abbreviated Injury Scale (head AIS < 3), whereas 83 and 52 patients had a severe injury of the chest and abdomen, respectively (Table 1). Most patients were admitted to the Acute Care Surgery/Trauma Service (82%). After propensity score matching, there were no statistically significant differences between their baseline characteristics and admission physiologic values (Table 1).

Table 2 shows the injury patterns of the study population. Patients in whom CDAI developed were statistically significantly more likely than those without CDAI to sustain a renal injury (10% vs 1%, p = 0.01), colonic injury (24% vs 3%, p < 0.01), or spinal injury (22% vs 10%, p = 0.03). Administration of clindamycin or of second-, third-, and fourth-generation cephalosporins were positively associated with significantly higher incidence of CDAI in the study population (Table 3). Clindamycin is generally administered in our hospital when a facial fracture is diagnosed during the workup. None of the patients who received clindamycin had a known penicillin allergy. All the patients who received clindamycin presented with a facial fracture. Similarly, the use of intravenous protein pump inhibitors resulted in a higher incidence of CDAI (24% vs 2%, p ≤ 0.01; Table 3).

The development of CDAI in trauma patients was associated with significantly higher morbidity and mortality. There was a 3-fold increase in the incidence of mortality for the CDAI group compared with their propensity-matched counterparts (12% vs 4%, p = 0.04). Similarly, the need for ventilator support, ICU length of stay, total ventilator days, and hospital length of stay were significantly higher for the CDAI group (Table 4).

To develop the CDIF score, we performed a forward stepwise logistic regression, and the β coefficients were derived from that model. Table 5 depicts the independent predictors of CDAI development derived from the regression model. Admission WBC, use of intravenous proton pump inhibitors, use of a third-generation cephalosporin, colonic injury, use of clindamycin, spinal injury, the need for surgical intervention after the injury, and the use of a fourth-generation cephalosporin were independently associated with CDAI development. The area under the curve (95% confidence interval) of the model was 0.96 (0.94-0.99), p < 0.01. The CDIF score was derived from the summation

Table 2. Patterns of injury

Injury	Overall (N = 200), no. (%)	*Clostridium difficile* positive (n = 50), no. (%)	*Clostridium difficile* negative (n = 150), no. (%)	p value
Intracranial injury	50 (25.0)	15 (30.0)	35 (23.3)	0.35
Pelvic fracture	10 (5.0)	0 (0)	10 (6.7)	0.07
Rib fractures	31 (15.5)	10 (20.0)	21 (14.0)	0.31
Pancreatic injury	2 (1.0)	2 (4.0)	0 (0)	0.06
Renal injury	7 (3.5)	5 (10.0)	2 (1.3)	0.01
Pneumothorax/hemothorax	28 (14.0)	9 (18.0)	19 (12.7)	0.35
Small-bowel injury[a]	17 (8.5)	7 (14.0)	10 (6.7)	0.14
Colonic injury[a]	16 (8.0)	12 (24.0)	4 (2.7)	< 0.01
Hepatic injury	7 (3.5)	4 (8.0)	3 (2.0)	0.07
Splenic injury	7 (3.5)	3 (6.0)	4 (2.7)	0.38
Long-bone injury	65 (32.5)	16 (32.0)	49 (32.7)	0.93
Spinal injury	26 (13.0)	11 (22.0)	15 (10.0)	0.03

[a] Excluding mesenteric hematomas that were observed.

Table 3. Antibiotic treatment before infection and peak white blood cell count[a]

Antibiotic	Overall (N = 200)	*Clostridium difficile* positive (n = 50)	*Clostridium difficile* negative (n = 150)	p value
Quinolones	7 (3.5)	1 (2.0)	6 (4.0)	0.68
Trimethoprim-sulfamethoxazole	7 (3.5)	1 (2.0)	6 (4.0)	0.68
Macrolides	6 (3.0)	4 (8.0)	2 (1.3)	0.04
Clindamycin	8 (4.0)	3 (6.0)	5 (3.3)	0.42
Penicillin	13 (6.5)	4 (8.0)	9 (6.0)	0.74
Aminoglycoside	8 (4.0)	2 (4.0)	6 (4.0)	> 0.99
Ertapenem	4 (2.0)	4 (8.0)	0 (0)	0.04
Linezolid	8 (4.0)	4 (8.0)	4 (2.7)	0.11
First-generation cephalosporin	79 (39.5)	25 (50.0)	54 (36.0)	0.08
Second-generation cephalosporin	29 (14.5)	12 (24.0)	17 (11.3)	0.04
Third-generation cephalosporin	15 (7.5)	12 (24.0)	3 (2.0)	< 0.01
Fourth-generation cephalosporin	20 (10.0)	12 (24.0)	8 (5.3)	< 0.01
IV PPIs	29 (14.5)	16 (32.0)	13 (8.7)	< 0.01
Admission WBC, mean (SD), $\times 10^9$/L	10.3 (6.1)	11.5 (5.1)	8.7 (6.2)	0.04

[a] Data are expressed as no. (%) unless otherwise indicated.
IV PPIs = intravenous proton pump inhibitors; SD = standard deviation; WBC = white blood cell count.

Table 4. Outcomes

Outcome	Overall (N = 200)	*Clostridium difficile* positive (n = 50)	*Clostridium difficile* negative (n = 150)	p value
Inhospital mortality, no. (%)	12 (6.0)	6 (12.0)	6 (4.0)	0.04
Need for ventilator support, no. (%)	66 (33.2)	28 (57.1)	38 (25.3)	< 0.01
ICU LOS, mean (SD), days	3.1 (0.5)	8.1 (4.1)	0.9 (0.3)	< 0.01
Ventilator days, mean (SD)	1.0 (0.2)	2.4 (0.2)	0.7 (0.1)	< 0.01
Hospital LOS, mean (SD), days	4.3 (2.1)	15.3 (1.4)	2.1 (0.6)	< 0.01

ICU = Intensive Care Unit; LOS = length of stay; SD = standard deviation

of the β coefficients of these variables, as depicted in Table 6. For assessment of the applicability of the model, the study population was subsequently divided into 5 groups on the basis of their CDIF score, and the probability of CDAI development was calculated for each group using the adjusted odds ratio (95% confidence interval) that was derived from the multivariate regression. The process was performed for both the derivation and the validation cohorts (Table 7). As the CDIF score increased, the probability of CDAI developing similarly increased (Figure 2).

Table 5. Independent predictors for *Clostridium difficile* infection

Step	Variable	Adjusted OR (95% CI)[a]	Adjusted p value	Cumulative R^2
1	Injury Severity Score	1.99 (1.62-2.24)	< 0.01	0.196
2	IV PPIs	1.24 (1.10-1.54)	< 0.01	0.231
3	Third-generation cephalosporin	1.28 (1.07-2.01)	< 0.01	0.285
4	Colonic injury	3.52 (1.08-15.32)	< 0.01	0.304
5	Clindamycin	19.80 (4.96-31.34)	< 0.01	0.329
6	Spinal injury	41.46 (5.39-47.06)	< 0.01	0.384
7	Operating room for trauma	9.41 (2.29-38.78)	0.02	0.406
8	Admission WBC	8.17 (1.65-23.10)	0.012	0.456
9	Fourth-generation cephalosporin	4.65 (1.07-20.32)	0.041	0.487

[a] Area under the curve (95% CI): 0.97 (0.94-0.99), p < 0.001.
CI = confidence interval; IV PPIs = intravenous proton pump inhibitors; OR = odds ratio; WBC = white blood cell count.

DISCUSSION

The present study findings suggest that CDAI is a rare occurrence in patients sustaining a traumatic injury. To our knowledge, this is the first study to report the creation of a scoring system to risk-stratify patients on the basis of their probability of CDAI developing after trauma.

In 1983, Trunkey[1] postulated a trimodal distribution of death in trauma patients. The first peak of death was caused by massive vascular or solid organ injury and central nervous system injury, and it primarily occurred at the scene. The second peak of death was caused by hemorrhage. These patients could potentially be saved by prompt resuscitation and identification of injuries in the trauma bay with appropriate intervention. The third peak of death was reported to occur days to weeks later and occurred because of multiorgan system failure and sepsis. The percentage of deaths in the first peak was 45%, second peak was 34%, and third peak was 20% in the original description of trimodal deaths.[1]

Since Trunkey's landmark study, multiple studies evaluated the trimodal distribution in the 21st Century at Level 1 Trauma Centers and found no trimodal distribution.[5-7] In comparison to Trunkey's[1] original 20% of trauma mortality cases being late deaths, Demetriades[8] found a reduction to 7.6%. With the advances in critical care and postoperative care, this number could potentially decrease if modifiable risk factors were identified. Prevention and early recognition/treatment of infection is critical in all patients. *C difficile* is the pathogen most commonly identified in cases of nosocomial antibiotic-associated diarrhea, and infection with this organism may have serious or even fatal consequences.[9] Outbreaks of *C difficile* are occurring more frequently and are associated with increasing rates of toxic megacolon, septic shock, and death.[10]

Although ample studies exist on the management and impact of CDAI in the general population, there is a paucity of data in the trauma patient population. In this study, we assess the effect of CDAI on trauma patients and present a scoring system to predict the development of CDAI.

In our study, we matched the patients with CDAI to the patients without CDAI using propensity score matching to ensure similar baseline characteristics and

Table 6. *Clostridium difficile* influencing factor score

Influencing factor	Points
ISS 16-24	5
ISS ≥ 25	10
IV PPIs	3
Third-generation cephalosporin	2
Colonic injury	2
Clindamycin	2
Spinal injury	1
Operating room for trauma	1
WBC < 15,000/μL	1

ISS = Injury Severity Score; IV PPIs = intravenous proton pump inhibitors; WBC = white blood cell count.

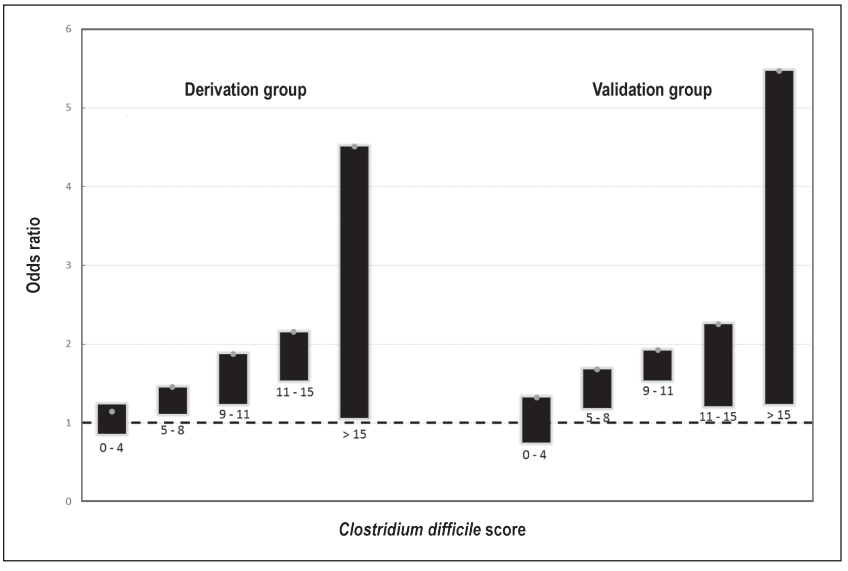

Figure 2. Probability of *Clostridium difficile* infection stratified by *C difficile* influencing factor score (derivation and validation cohorts).

Table 7. Probability of development of *Clostridium difficile* infection stratified by *Clostridium difficile* influencing factor score

Score	Derivation cohort, adjusted OR (95% CI)[a]	Validation cohort, adjusted OR (95% CI)[b]
0-4	1.23 (0.86-1.41)	1.14 (0.75-0.32)
5-8	1.25 (1.11-1.45)	1.32 (1.19-0.68)
9-11	1.56 (1.24-1.87)	1.72 (1.54-0.92)
12-15	1.87 (1.54-2.15)	1.75 (1.21-0.25)
> 15	2.25 (1.06-4.51)	1.98 (1.24-5.47)

[a] C statistic for derivation cohort: 0.75 (95% OR 0.71-0.82), p < 0.01.
[b] C statistic for validation cohort: 0.69 (95% OR 0.67-0.71), p < 0.01.
CI = confidence interval; OR = odds ratio.

demographics. Our results show that trauma patients in whom CDAI developed had significantly higher mortality, need for mechanical ventilation, and hospital length of stay, which leads to increased direct and indirect costs.

The overall US costs of *C difficile* were close to $1.1 billion annually in one study[11] and $3.2 billion annually in another study.[12] Even when compared with other infections, CDAI is very expensive. The costs of CDAI range from $2000 to $72,000 per case,[13,14] compared with methicillin-resistant *Staphylococcus aureus,* which costs between $5000 and $40,000.[15]

Our CDIF score was created using 9 factors and assigning specific points for each. These points are then added to give a score, and the probability of CDAI development is predicted (Tables 6 and 7). For example, if a patient had a colonic injury, went to the operating room for trauma, and had a WBC greater than 15,000/μL (> 15 × 10^9/L), his/her composite score would be 4. The corresponding probability of CDAI development is above 80% (Table 7). With this information, clinicians can be hypervigilant about early detection and prompt treatment. There are many causes of diarrhea in trauma patients, so having a scoring system with the probability of CDAI development can be very useful. In addition, as with any infectious disease, early recognition of the risk and prevention of the development of *C difficile* infection may be of more importance than early recognition and treatment. For example, a patient with high CDIF score could raise the index of suspicion of the rounding physician, who then could institute a series of interventions (ie, early termination of antibiotics and/or initiation of CDAI-appropriate hand hygiene) to not only prevent that specific patient from having an infection but also spreading the infection to surrounding patients. The utility of the CDIF score to prevent an infection might indeed be its most important clinical function.

CONCLUSION

Our study demonstrated significantly higher morbidity and mortality in the setting of a traumatic injury with the development of CDAI. Our scoring system can be used to predict the probability of CDAI development after a traumatic injury, and it hopefully can guide clinicians when patients experience diarrhea. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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