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Clostridium difficile Infections after Blunt Trauma: A Different Patient Population?

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Abstract

Background: The epidemiology of *Clostridium difficile*-associated infection (CDI) has changed, and it is evident that susceptibility is related not only to exposures and bacterial potency, but host factors as well. Several small studies have suggested that CDI after trauma is associated with a different patient phenotype. The purpose of this study was to examine and describe the epidemiologic factors associated with *C. difficile* in blunt trauma patients without traumatic brain injury using the Trauma-Related Database as a part of the ''Inflammation and Host Response to Injury'' (Glue Grant) and the University of Florida Integrated Data Repository.
Methods: Previously recorded baseline characteristics, clinical data, and outcomes were compared between groups (67 *C. difficile* and 384 uncomplicated, 813 intermediate, and 761 complicated non-*C. difficile* patients) as defined by the Glue Grant on admission and at days seven and 14.
Results: The majority of CDI patients experienced complicated or intermediate clinical courses. The mean ages of all cohorts were less than 65 y and CDI patients were significantly older than uncomplicated patients without CDI. The CDI patients had increased days in the hospital and on the ventilator, as well as significantly higher new injury severity scores (NISS), and a greater percentage of patients with NISS >34 points compared with non-CDI patients. They also had greater Marshall and Denver multiple organ dysfunction scores than non-CDI uncomplicated patients, and greater creatinine, alkaline phosphatase, neutrophil count, lactic acid, and P_iO_2: F_iO_2 compared with all non-CDI cohorts on admission. In addition, the CDI patients had higher glucose concentrations and base deficit from uncomplicated patients and greater leukocytosis than complicated patients on admission. Several of these changes persisted to days seven and 14.
Conclusion: Analysis of severe blunt trauma patients with *C. difficile*, as compared with non-CDI patients, reveals evidence of increased inflammation, immunosuppression, worse acute kidney injury, higher NISS, greater days in the hospital and on the ventilator, higher organ injury scores, and prolonged clinical courses. This supports reports of an increased prevalence of CDI in a younger population not believed previously to be at risk. This unique population may have specific genomic or inflammation-related risk factors that may play more important roles in disease susceptibility. Prospective analysis may allow early identification of at-risk patients, creation of novel therapeutics, and improved understanding of how and why *C. difficile* colonization transforms into infection after severe blunt trauma.

Clostridium difficile is a cause of infectious diarrhea and pseudomembranous colitis and is well recognized as a factor that can impact hospital outcomes [1,2]. Although the disease, most of which is not fulminant, has classically had minimal impact on mortality ($<2\%$), the health care burden from management and complications attributed to the disease is high [3]. In fact, in one year alone in the United States, an estimated $3.2 billion was spent on *C. difficile*-associated diarrhea [4–6].

Effort has been made to describe the epidemiology and risk factors for *C. difficile* infection (CDI). Historically, well-accepted risk factors included antibiotic use, increased age (older than 65 y), as well as previous exposure to hospitals or nursing home facilities [1]. Although many patients meet

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these criteria, the majority of hospitalized patients colonized with the bacteria and those receiving antibiotics never develop the disease [7], making it evident that the pathway that leads to the development of infection is still unclear.

In recent years, the epidemiology of CDI has altered as increased reports of rising incidence, severity, resistance, mortality, and complications associated with CDI have come to light [5,6,8]. Simultaneously, it was reported that a new population, lacking traditional risk factors, may be at risk for development of CDI. With the discovery of this new patient population afflicted with CDI, it is becoming increasingly clear that susceptibility to infection is affected not only by environmental exposures and the potency of the bacterium, but host factors as well [9].

The trauma population is on average, a young population, with relative immune suppression because of injury [10], often without previous long-term antibiotic exposure or exposure to health care facilities. To date, there have been few studies looking at *C. difficile* in the trauma population and those that have, report only a small sample size. The largest studies to date are by Lumpkins et al. and Efron et al. who reported sample sizes of 19 and 21, respectively [9,11,12]. Incidence of CDI in the trauma population has been reported to be similar to that observed in the hospitalized population [12], which is surprising because demographics of trauma populations do not match the standard risk profile for CDI (age, hospital exposure, and antibiotics). Lumpkins et al. [12] reported a significantly younger population of patients diagnosed with *C. difficile,* which was also associated with increased hospital and intensive care unit (ICU) lengths of stay (LOS). In addition, they reported CDI in trauma patients without antibiotic exposure, supporting the hypothesis that *C. difficile* after trauma may be associated with a different patient phenotype.

The purpose of this study was to examine and describe the epidemiologic factors associated with *C. difficile* in blunt non-traumatic brain injury (TBI) trauma patients using the Trauma-Related Database (TRDB) and University of Florida (UF) Integrated Data Repository, allowing analysis of a larger cohort of trauma patients than described previously in the literature.

Patients and Methods

Before initiation of this project, approval was obtained from the UF Institutional Review Board to analyze data collected in the UF Integrated Data Repository as a retrospective cohort study, and de-identified data collected from the Glue Grant TRDB.

Data source and study population

This is a multi-institution, retrospective cohort study, looking for nosocomial infections. The Inflammation and Host Response to Injury (Glue Grant) is a collaborative, large-scale, interdisciplinary research program created to better describe the different clinical outcomes after traumatic injury. The TRDB was developed as part of this program and contains de-identified, prospectively collected clinical and gene expression data from patients with severe blunt trauma without TBI. Inclusion criteria for the Glue Grant included severe (injury severity score >15) non-TBI blunt trauma patients, older than 16 y, who presented with evidence of shock (systolic blood pressure <90 mm Hg) or acidosis (base deficit ≥ 6 mEq/L) and required resuscitation with blood products. Patients were enrolled from eight participating American College of Surgeons designated level I trauma centers. We reviewed the clinical data obtained previously from the 2,006 patients identified as having blunt trauma injury in the TRDB between 2001 and 2012.

Patients found as not developing *C. difficile* in the TRDB were used for comparison. These patients were separated into three main groups—complicated, intermediate, and uncomplicated—based on clinical parameters used to determine their time to organ recovery (TTR) [13]. Clinical courses were considered uncomplicated if they had a TTR of less than 4 d without development of multiple-organ failure (MOF) ($n=382$) and a complicated course was defined as a TTR greater than 14 d with development of MOF or late death ($n=761$). Patients who fell between the complicated and uncomplicated causes were considered to have intermediate outcomes ($n=813$). Exact methods for calculating TTR were reported previously in the literature [13]. *Costridium difficile* patients in the TRDB were distinguished by the presence of a positive *C. difficile* real-time polymerase chain reaction (RT-PCR) (48 patients, with one patient with two reported episodes).

We also reviewed data collected previously from adult surgical patients in the UF Integrated Data Repository from 2006–2010. The University of Florida did not become a level I designated trauma center until 2006 so this was chosen as a cutoff point. The UF and Shands Hospital have a 75-bed multidisciplinary surgical ICU where critically ill adult surgical patients are managed by intensivists. This patient population comprises surgical, trauma and burn, neurosurgical, and cardiovascular surgery patients. The billing database for the UF and Shands Hospital was established in 1990, and provides information on patients' demographics, outcomes, and hospital characteristics for all discharged patients. The database also provides International Classification of Diseases, Ninth edition, Clinical Modification (ICD-9-CM) codes that are listed for each admission and allow access to a wealth of information on critically injured surgical patients.

To obtain our trauma population we first cross-referenced the UF Trauma Center Registry with the UF integrated database to identify trauma patients enrolled in the Repository between the years designated. A total of 3,036 trauma patients were found in the database over the four years referenced. In this trauma patient population, we identified patients with nosocomial *C. difficile* infections by searching for those with recorded diagnosis for *C. difficile* based on ICD-9-CM code 008.45. The patients' electronic medical records (EMRs) were also reviewed for concurrent positive RT-PCRs for *C. difficile* during the patients' hospital stays. If a discrepancy was noted between the reported diagnosis and the RT-PCR, the patients were excluded from the study. A total of 19 *C. difficile* patients were identified increasing the total *C. difficile* patient number to 67. The complete EMRs of the 19 patients were reviewed and relevant demographic and clinical data pertinent to that hospital admission were collected.

The UF was one of the original participants in the Glue Grant study and although a relatively small number of patients were enrolled from our institution before 2010, we examined the two databases to ensure there was no patient overlap. To do this we reviewed the institutional enrollment codes for the *C. difficile*

patients obtained from the Glue Grant that confirmed that none of the patients identified from the TRDB were enrolled from our institution and therefore were distinct from the additional patients collected in the UF repository.

Clinical outcomes and laboratory analysis

Patient demographics and outcomes were recorded, including: Age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, new injury severity score (NISS), survival, day of infection diagnosis, hospital length of stay (HLOS), maximum abbreviated injury score (AIS), and number of ventilator-dependent days. These parameters were compared between *C. difficile* patients and non-*C. difficile* patients with complicated/intermediate courses combined, as well as to the non-*C. difficile* uncomplicated cohort.

Next, we looked at clinical parameters recorded on admission and on days seven and 14 for *C. difficile* patients, as well as non-*C. difficile* patients undergoing complicated or intermediate courses. For uncomplicated non-*C. difficile* patients, the worst values over their hospital course were used for comparison. Parameters recorded included values for: Marshall score, Denver score, creatinine, glucose, highest lactate and base deficit, bilirubin, alkaline phosphatase, albumin, white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, P_iO_2:F_iO_2 (P:F) ratio, and international normalized ratio (INR).

To address the possibility that differences observed among groups may be confounded by early mortality, we reanalyzed the groups in similar fashion to above after excluding patients who had died early. The Glue Grant previously considered death within 72 h of admission to represent early mortality, and this cutoff was used to define early mortality among the cohorts in our population.

Statistical analysis

We used multivariable logistic regression (MLR) to model the association between demographic and clinical characteristics at admission and the occurrence of CDI in the population excluding early mortality. We selected clinical parameters to be included in the model based on their significance in a prior univariate analysis. Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were reported for each parameter. We used the area under the receiver-operating characteristic curve (AUC ROC) values and Hosmer-Lemeshow goodness-of-fit test to assess model calibration and discrimination.

Frequencies of categorical variables were reported as a percentage and the Pearson χ^2 test or Fisher exact test was used to test independence between categorical variables as appropriate. None of the continuous variables satisfied a normality assumption that was tested using the Kolmogorov-Smirnov test, hence medians and 25th and 75th percentiles were recorded and the Kruskal-Wallis test was used for comparisons. A two-sided $p < 0.05$ was considered significant for all tests performed. Statistical analysis was performed with SAS (version 9.3, SAS Institute, Cary, NC).

Results

Analysis of patient demographics and baseline characteristics revealed that a total of 67 of 5,042 patients developed

TABLE 1. COMPARISON OF PATIENT CHARACTERISTIC AND CLINICAL OUTCOMES BETWEEN *CLOSTRIDIUM DIFFICILE* AND NON-*CLOSTRIDIUM DIFFICILE* COHORTS

		Non-C. difficile					
	C. difficile (n = *67*)	*All non*-C. difficile (n = *1,956*)	*Complicated/ intermediate* (n = *1,574*)	*Uncomplicated* (n = *382*)	p[a]	p[b]	p[c]
Demographics and baseline characteristics							
Female, n (%)	17 (25.4%)	656 (34%)	515 (32.7%)	141 (36.7%)	0.167	0.212	0.073
Age, Median (25th, 75th)	43.9 (18, 90)	41 (26, 55)	43.9 (3, 90)	37.5 (11, 90)	0.686	0.933	0.024
Mean (min, max)	44 (18, 90)	43 (3, 90)	44 (3, 90)	38 (11, 90)			
NISS, Median (25th, 75th)	38 (27, 48)	32 (26, 41)	32 (27, 43)	27 (22, 38)	0.008	0.032	< 0.0001
NISS > 34, n (%)	38 (56.7%)	674 (34%)	573 (36.4%)	103 (26.8%)	0.0002	0.001	< 0.0001
Day of diagnosis, Median (25th, 75th)	10 (7, 16)	NA	NA	NA	NA	NA	NA
Max AIS, Median (25th, 75th)	5 (4, 5)	4 (3, 5)	4 (4, 5)	4 (3, 4)	0.004	0.027	< 0.0001
Clinical outcomes							
Hospital mortality, n (%)	4 (6%)	315 (16%)	312 (20%)	3 (1%)	0.026	0.005	0.011
Hospital length of stay, Median (25th, 75th)	29 (21, 42)	18 (10, 30)	21 (12, 33)	10 (7, 15)	< 0.0001	< 0.0001	< 0.0001
Ventilation days, Median (25th, 75th)	14 (7, 22)	6 (2, 13)	8 (4, 15)	2 (1, 2)	< 0.001	0.0003	< 0.0001

Note: p[a] compares *C. difficile* and all non-*C. difficile* patients; p[b] compares *C. difficile* patients with complicated/intermediate non-*C. difficile* patients; p[c] compares *C. difficile* patients with uncomplicated non-*C. difficile* patients.
NISS = new injury severity score; AIS = abbreviated injury score; NA = not applicable.

Table 2. Comparison of Patient Clinical Characteristics between *Clostridium difficile* and Non-*Clostridium difficile* Cohorts

Clinical characteristics	C. difficile *(n=67)*	*Non*-C. difficile			p[a]	p[b]	p[c]
		All non-C. difficile *(n=1,956)*	*Complicated/ intermediate (n=1,574)*	*Uncomplicated (n=382)*			
Admission							
Marshall Score	6.0 (4.7, 8,2)	4.8 (3.3, 6.8)	5.5 (4.1, 7.3)	2.4 (1.7, 3.3)	0.000	0.053	<0.0001
Denver Score	2 (1.5, 3)	2 (1, 3)	2 (1, 4)	0 (0, 1)	0.134	0.890	<0.00001
Creatinine (mg/dL)	1 (0.8, 1.3)	1 (1, 1)	1 (1, 1)	0.8 (0.7, 0.9)	0.586	0.003	<0.0001
Alk phos (u/L)	136 (76, 219)	51 (41, 64)	50 (40, 62)	55 (47, 79)	<0.0001	<0.0001	0.000
Albumin (g/dL)	2.3 (1.6, 2.7)	2.1 (1.8, 2.4)	2 (1.8, 2.4)	2.3 (2, 2.6)	0.368	0.233	0.561
WBC (1,000/mcL)	13.5 (8.9, 19.6)	11.7 (8.7, 15.9)	10.3 (7.3, 14.7)	13 (9.8, 16.7)	0.104	0.003	0.715
Neutrophil count (1,000/mcL)	16.4 (7.0, 11.0)	10.6 (7.1, 13.6)	10.6 (7.0, 13.6)	10.9 (7.3, 13.6)	<0.0001	<0.0001	<0.0001
Lymphocyte count (1,000/mL)	2.0 (1.0, 5.0)	1.3 (0.7, 7.1)	0.9 (0.6, 1.5)	0.9 (0.7, 1.2)	0.002	<0.0001	<0.0001
Platelet count (1,000/mm^3)	99.5 (83, 134)	101 (80, 128)	96 (78, 121)	129 (109, 158)	0.413	0.068	<0.0001
P:F (per unit change)	169 (100, 270)	221 (150, 306)	219 (147, 302)	312.5 (225, 360)	0.008	0.014	<0.0001
Glucose (mg/dL)	207.5 (164, 249.5)	191 (161, 242)	201 (166, 250)	171 (147, 198)	0.907	0.457	0.017
Lactate (mmol/L)	5 (3.5, 6.9)	2.9 (2.0, 4.4)	3.1 (2.1, 4.7)	2.2 (1.4, 2.8)	<0.0001	<0.0001	<0.0001
Base deficit (mEq/L)	−9.7 (−11.9, −7.7)	−9.9 (−13.1, −7.0)	−10.2 (−14, −7)	−8 (−10.4, −6)	0.785	0.331	0.009
Hospital day 7							
Marshall Score	5 (5, 8)		5 (2, 7)			0.005	
Denver Score	3 (1, 4)		0 (0, 1)			<0.0001	
Albumin (g/dL)	2.1 (1.7, 2.4)		1.8 (1.5, 2.1)			0.020	
WBC (1,000/mcL)	12.4 (8.8, 18.2)		12.6 (9.5, 16.8)			0.880	
Neutrophil count (1,000/mcL)	12.4 (7.9, 11.7)		10.8 (7.2, 13.3)			0.029	
Lymphocyte count (1,000/mL)	2.6 (1.2, 6.5)		1.21 (0.8, 1.7)			0.001	
P:F (per unit change)	228 (132, 272)		211 (162, 283)			0.517	
Hospital day 14							
Marshall Score	5 (4, 7)		3 (0, 5)			<0.0001	
Denver Score	2 (1, 4)		0 (0, 0)			<0.0001	
Albumin (g/dL)	1.9 (1.7, 2.6)		1.8 (1.5, 2.1)			0.067	
WBC (1,000/mcL)	15 (11.8, 19.9)		14.6 (10.9, 18.1)			0.335	
Neutrophil count (1,000/mcL)	15.9 (7.5, 11.8)		11.2 (7.7, 13.9)			0.000	
Lymphocyte count (1,000/mL)	6.2 (2.1, 9.0)		1.4 (1, 2)			<0.0001	
P:F (per unit change)	244.5 (184, 328)		213 (158, 274)			0.062	

Note: All values represent medians and the 25th and 75th percentiles unless otherwise specified. p[a] compares *C. difficile* and all non-*C. difficile* patients; p[b] compares *C. difficile* patients with complicated/intermediate non-*C. difficile* patients; p[c] compares *C. difficile* patients with uncomplicated non-*C. difficile* patients' worst values over their stay.

WBC = white blood cell count; alk phos = alkaline phosphatase; P/F ratio, P_iO_2/F_iO_2 ratio.

C. difficile-associated diarrhea during their hospitalization (2% and 1% for the TRDB and UF populations, respectively). The mean age of both the *C. difficile* and non-*C. difficile* cohorts was less than 65 y (43.9 ± 19.9 and 42.7 ± 18.7, respectively) and the *C. difficile* population was significantly older than the uncomplicated non-*C. difficile* patients (37.5 ± 15.7 y). The median number of hospital days to *C. difficile*-diagnosis was 10, with two patients noted to have infection diagnosed early in their hospital course (day three). Both the maximum AIS and NISS were significantly higher in the patients with CDI compared with all non-*C. difficile* patients and individual non-*C. difficile* cohorts. The CDI patients also had a significantly higher percentage of patients with NISS >34 points (57%) compared with all cohorts (Table 1). On re-analysis, these results continued to be significant between CDI and non-CDI cohorts even after excluding early mortality patients (supplementary Table S1; supplementary data are available at www.liebertpub.com/sur).

The clinical outcomes of these patients support previous reports that patients who developed CDI have significantly greater HLOS and ventilator-dependent days than non-CDI patients in all groups compared. The mortality for the *C. difficile* population in our study was 6%, significantly lower than non-CDI complicated/intermediate patients (20%) and higher than the non-CDI uncomplicated patients (1%) (Table 1). When re-analyzed to exclude those who died with early-onset mortality, the mortality rate was decreased from 20% to 11% in the non-CDI complicated/intermediate patients and was no longer significantly different from that observed in the *C. difficile* population.

When comparing the clinical data on admission, CDI patients had significantly higher Marshall and Denver scores, glucose concentrations, and base deficits from uncomplicated patients' worst values over their stay and significantly greater leukocytosis compared with complicated/intermediate patients. They also had significantly higher values of creatinine, alkaline phosphatase, neutrophil counts, International Normalized Ratio (INR) of prothrombin time, lactic acid, and P:F compared with either uncomplicated or complicated/intermediate non-CDI cohorts. Compared with complicated/intermediate non-*C. difficile* individuals at hospital days seven and 14, *C. difficile* patients had significantly higher Marshall and Denver scores and neutrophil and lymphocyte counts out to day 14. *C. difficile* patients had persistently low albumin concentrations (<3 g/dL) and leukocytosis over the 2 wks recorded, although not significantly more so than the non-CDI complicated/intermediate cohort (Table 2). Clinical data analysis among the cohorts, when excluding patients who died prior to 72 h, showed similar results for the parameters examined when compared with the original analysis with a few notable exceptions. Looking at the parameters recorded on admission, both Marshall and Denver scores were significantly increased in CDI patients when compared with all non-CDI patients. Also, the significantly higher Marshall scores and platelet counts observed between the complicated/intermediate non-*C. difficile* and the CDI cohorts were no longer observed after excluding early mortality patients. On day 14, the P:F and albumin concentration were significantly lower in the complicated/intermediate non-*C. difficile* groups compared with patients with *C. difficile* (supplementary Table S2).

We constructed a MLR model to determine demographic and clinical characteristics associated with the occurrence of CDI in the blunt trauma population. The increasing P/F ratio and lactate concentrations were significantly associated with CDI with odds ratios of 1.01 (95% CI 1.001–1.01) and 1.37 (95% CI 1.19–1.59) for each one unit increase, respectively. The model had good discrimination with an AUC of 0.74 (95% CI 0.64–0.83) and showed sufficient fit with a Hosmer-Lemeshow p value of 0.637 (Table 3).

Table 3. The Association between Demographic and Clinical Characteristics of Patients and *Clostridium difficile* by Multivariable Logistic Regression

Model fit	***C. difficile***
AUC ROC (95% CI)	0.74 (0.64, 0.83)
Hosmer-Lemeshow Goodness-of-Fit Test p-value	0.637
Variables	***Odds ratio (95% CI)***
Age (per 1 y increase)	1.004 (0.99–1.02)
Male gender (vs. female)	1.54 (0.68–3.46)
Admission NISS (per 1 unit increase)	1.02 (0.99–1.05)
Admission Marshall Score (per 1 u increase)	1.08 (0.95–1.23)
Admission INR (per 1 u increase)	0.78 (0.43–1.4)
Admission P:F (per 1 u increase)	1.01 (1.001–1.01)[a]
Admission lactate (per 1 mmol/L increase)	1.37 (1.19–1.59)[a]

p[a]-value < 0.05. Statistically significant variables with p-value <0.05 are shown in bold.

AUC ROC = area under the receiver-operating characteristic curve; CI = confidence interval; INR, international normalized ratio; P:F = P_iO_2:F_iO_2 ratio; NISS = new injury severity score.

Discussion

In recent years, the rate of CDI has tripled [5] and the mortality rate has quadrupled [6]. Additionally, a new, more virulent strain has been identified [5] correlating with the U.S. Centers for Disease Control and Prevention statement describing reports characterizing a new population of patients afflicted by CDI that had been believed previously to be at low risk [14]. This population includes a younger age group, with little-to-no antibiotic exposure or previous hospitalization [5,12,14]. These changes may be related in some way to the new strain of *C. difficile*, however, no evidence has shown an association between the new strain and this evolving clinical picture [15].

Although *C. difficile* after trauma has been reviewed previously [12,16], this is the largest current review of prospectively obtained data on CDI after severe blunt trauma. The mean age for our *C. difficile* population is representative of the standard age for trauma patients, but is significantly younger than that commonly accepted for CDI patients [5,12,16,17]. We found the prevalence of *C. difficile* infection in our patients to be lower than the 3% reported in the general hospital population [18], as well as that reported previously in the trauma population by Lumpkin et al. [12]. This lower prevalence most likely represents a more accurate reflection in this population given the relatively small sample size of previous studies. Regardless, the prevalence is higher than one would expect when considering the age of the population studied, supporting reports of a new population at risk.

Preliminary evidence appears to support that host factors play a role in the pathogenicity of CDI [5], including several reports of the role of immunosuppression in increasing susceptibility in populations without previous antibiotic exposure [6,12]. Background for this includes studies on post-transplant patients with active immunosuppression as well as patients undergoing oncologic therapy who are at increased risk for CDI despite the lack of exposure to antimicrobial [6]. Co-morbidities known to affect the immune response have also been shown to be associated with *C. difficile* [17,19], which may explain the increased risk in the aging population, which is known to undergo immunosenescence [16,20]. In addition, specific genetic polymorphisms have been shown to be associated with increased risk for development of primary infection with *C. difficile,* as well as recurrences [12,14,21–23].

In fact, using microarray analysis from the TRDB looking at genomic profiles of circulating leukocytes in blunt trauma patients, we determined recently that early in the patients' hospital courses, there was a change in genetic expression after development of CDI not observed in those who never develop infection [9]. Many of the changes observed were related to response to inflammation and host adaptive immunity. More importantly, early microarray analysis demonstrated the potential to predict which patients were going to develop CDI. Although these data still require prospective validation, it supports the hypothesis that inherent host factors, i.e., an individual's genetic profile and subsequent response on the individual's immune system and inflammation, may represent a predisposed vulnerability to infection not recognized previously [9].

There was a significantly higher mortality rate for our *C. difficile* patients compared with previous reports of that attributed to CDI ($<2\%$) which could not be explained even after taking into account early mortality due to severity of injury [3]. Our data are consistent with other reports of CDI being associated with increased HLOS and ventilator days [6]. This may not be surprising given that the population studied comprised a cohort of critically injured patients admitted in shock. The critical nature of the population is supported further by the significantly higher AIS, NISS, Marshall and Denver scores, which combined, represent markers associated with increased critical illness, prolonged time to recovery [19], worsening immune dysfunction [24–27], increased mortality, and worse clinical outcomes overall [19,28]. Marshall and Denver scores are measurements used to evaluate multiple-organ dysfunction syndrome that have been valid and are indicators of adverse outcomes in critical illness [29]. There has also been suggestion that CDI, in general, represents a marker for poor outcome [4].

Previous studies from the TRDB by Xiao et al. [30] looking at genomic data from blood leukocytes, have showes that severe blunt trauma patients undergoing complicated clinical courses have simultaneous suppression of genes involved in innate immunity, as well as increased gene expression in adaptive immunity that persists in duration and magnitude compared with patients undergoing uncomplicated courses. We found the majority of *C. difficile* patients (96%) from the TRDB underwent complicated or intermediate clinical courses, supporting the previous idea that they were injured more severely. Given the nature of the trauma population studied, it is not surprising that our clinical data mirror similar patterns as those reported previously in the trauma patients undergoing complicated courses. Overall, combined with the previous reports, our findings make for compelling evidence that individual host factors, such as genomic profiles and subsequent response to inflammation and immune response, might play a more important role in disease susceptibility than recognized previously.

There are several limitations of the present study. First, data on timing and specific antibiotic use were not recorded in the TRDB during the study, making it impossible at this time to determine a patient's antibiotic exposure in relation to diagnosis with *C. difficile*. Next, many parameters were not recorded consistently over the entire study group in the TRDB, which may skew the actual effect these parameters have between groups. Finally, this is a retrospective study looking only at the blunt trauma population and prospective analysis is still needed for further review.

In conclusion, our data suggest that blunt trauma patients who develop CDI are a unique population who may have specific genomic- or inflammation-related risk factors that make them susceptible to the disease. Given the increasing incidence and severity of infection combined with increasing numbers of long-term critically ill trauma patients, the ability to identify rapidly patients at risk and intervene is important for improving morbidity and decreasing heath care cost in the future. Further prospective analysis may allow early identification of patients at risk, as well as a better understanding of how or why *C. difficile* colonization transforms to infection, and hopefully lead to the creation of novel therapeutics.

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Author Disclosure Statement

The authors have nothing to disclose.

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