Published in final edited form as:

Surgery. 2016 June ; 159(6): 1631–1637. doi:10.1016/j.surg.2016.01.004.

Morbidity and Mortality in Severely Burned Children with *Clostridium Difficile*-Associated Diarrhea

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Abstract

Background—*Clostridium difficile* is a key culprit underlying nosocomial infectious diarrhea. We investigated the effect of *C. difficile*-associated diarrhea (CDAD) on morbidity and mortality in severely burned children and CDAD risk factors.

Methods—After review of 2,840 records, 288 pediatric burn patients were identified as having stool output exceeding $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for two or more successive days and had stool samples immunoassayed for Toxin A and B. A case-control analysis was performed by matching cases to controls via logistic regression and propensity scores so that age, admission time, and time of occurrence could be controlled; the endpoints were mortality and hospitalization time.

Results—Eighteen patients tested positive for *C. difficile* toxins [median age, 4 years; mean total body surface area (TBSA) burned, 59%]. In the CDAD group, unadjusted in-hospital mortality was 28% (OR=5.4, CI=1.7–16.7, $P=0.01$). Hospitalization averaged 48 days in the CDAD group and 38 days in the non-CDAD group ($P=0.24$). Length of stay per percent TBSA burned was greater in the CDAD group (0.82 ± 0.4 vs. 0.60 ± 0.4 , $P=0.03$), as were prolonged bouts of diarrhea complicated by acidosis (13 ± 16 vs. 4 ± 5 days, $P<0.005$). Of the 18 possible risk factors evaluated, inhalation injury diagnosed at admission occurred more often in CDAD patients than matched controls (59% vs. 31%, $P=0.04$).

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This work was presented at the 41st Society of Critical Care Medicine congress in Houston, Texas (February 2012).

Conclusions—CDAD during hospitalization is associated with greater mortality after burns. Inhalation injury increases the likelihood of *C. difficile* infection. Whether *C. difficile* infection is an indication of greater illness among certain burned patients is unknown.

Keywords

Clostridium difficile; diarrhea; children; burns; colitis

Introduction

Recently, *Clostridium difficile* has attracted the interest of the North American medical community due to an uptick in *C. difficile* infections associated with death. This spore-forming gram-positive anaerobe now accounts for most cases of hospital-acquired diarrhea.¹ *C. difficile* infection commonly occurs as a result of altered normal bacterial flora secondary to broad-spectrum antibiotic use in immune compromised patients (*e.g.*, critically ill patients, burn patients, and cancer patients receiving chemotherapy) and patients using medications such as proton pump inhibitors (PPIs).² *C. difficile* is associated with many complications such as toxic megacolon, pseudomembranous colitis, sepsis, or even death. These infections are difficult to treat because of the serious nature of *C. difficile*-induced illness. The exponential increase in infections over the past decade and the evolution of more virulent strains has made treatment even more challenging.³

The incidence of *C. difficile*-associated diarrhea (CDAD) remains unclear in children, let alone pediatric burn patients. *C. difficile* infection occurs at an incidence of roughly 4% in the ICU.⁴ For burn patients, the incidence has been reported to be between 1 and 17%.^{5,6} In 2002, Still and colleagues⁶ reported a CDAD incidence of 1% based on detection of *C. difficile* toxin A, the primary criterion used to diagnose CDAD. Crabtree and coworkers⁷ reported that more patients tested positive for *C. difficile* toxin at burn center ICUs than at non-burn ICUs. As no one has evaluated the incidence of CDAD in the pediatric burn population, we conducted a retrospective cohort analysis of all patients admitted to our pediatric burn ICU in order to investigate the incidence and outcomes of CDAD in the massively burned children as well as to identify CDAD risk factors in this population.

Methods

Study population

We accessed records from 6,053 first time encounters occurring over a 12-year period at Shriners Hospitals for Children—Galveston (Galveston, Texas). Of these, 3,343 admissions were reviewed and 2,840 were analyzed (Figure 1). Patients meeting the following criteria were included in our analyses: age of < 18 years, > 30% total body surface area (TBSA) burns (all burn patients requiring an admission), no signs of sepsis at admission, and transferred to our institution within 72 hours post injury. Patients were allocated into the diarrhea group or non-diarrhea group based on daily stool output. The diarrhea group had a daily stool output exceeding 10 ml/kg/day over 2 or more consecutive days.⁸ All patients with high stool output had stool analyzed for *C. difficile* toxins. Other commonly seen signs and symptoms in patients with diarrhea such as fever, leukocytosis, abdominal distension,

and significant amount of gastric residual volume necessitating holding tube feeding were recorded, along with patient demographics (*e.g.*, age, ethnicity, burn size, and length of hospitalization).

Case-control and case-cohort matching

Patients testing positive for *C. difficile* were matched to two comparison groups for two separate analyses, a case-control analysis and case-cohort analysis. Case-control analysis was used to uncover risk factors for *C. difficile* infection and case-cohort analysis to evaluate outcomes (death and other complications) of patients who acquired *C. difficile*. The data distribution was analyzed using QQ plots and the Kolmogorov-Smirnov normality test. Normally-distributed data are presented as mean $\pm$ SD or SEM and non-normally distributed data as median $\pm$ MAD.

For both analyses, we used SAS 9.2 to match cases to controls, in a blinded manner, at a 1:4 ratio according to the nearest matching propensity score. Logistic regression was used to calculate propensity scores. CDAD status served as the response variable. For case-control matching, predictors were admission within 7 days post burn and number of days at risk. One case did not match to any controls and was excluded from this arm of the study (Figure 1). For case-cohort matching, predictors included percent TBSA burned, percent third-degree burns, inhalation injury, and admission within 7 days post burn. For both analyses, matching was blindly performed in a 1:4 ratio according to the nearest propensity matching score. The quality of the matching was tested and examined. $P < 0.05$ was accepted as significant.

Results

Two thousand eight hundred and forty patients were admitted to the burn ICU over the course of a 12-year period (Figure 1). Of these, 289 (10.2%) experienced one or more episodes of diarrhea during their ICU stay. Stool samples from these patients were analyzed for *C. difficile* toxin. Eighteen (6.0%) of the 289 patients with diarrhea had stool samples that tested positive for *C. difficile* toxin (CDAD group), yielding an overall incidence of 0.6%. Patients' characteristics are presented in Table 1. Symptoms of infection with *C. difficile* were a combination of diarrhea with fever and leukocytosis. On average, a high stool output of 13–86 ml/kg/day was observed in patients with CDAD. None of the patients with CDAD required surgical intervention for toxic megacolon or colitis, a rare but fatal complication of the disease.⁹ All patients were treated with oral metronidazole for at least 10 days, and all patients tested negative in repeat stool toxin assays performed for recurring diarrhea while patients received therapy.

The 270 patients who did not have *C. difficile* toxins detected in their stool were categorized as the non-CDAD group. These patients were allocated among two groups, and case-control and case-cohort matching were conducted.

Demographics for the matched case controls are shown in Table 2. Sixty-eight patients were selected based on propensity scoring with similar scores. The CDAD group had a

significantly higher incidence of inhalation injury and lower incidence of fluoroquinolone use. PPIs were not associated with an increase in *C. difficile* infection (Table 2).

Matched cohort patient information is shown in Table 3. Patients were matched 1:4. Compared to control patients (6.5 ± 5 years and $58 \pm 22\%$ TBSA burned), the CDAD group had greater length of ICU stay normalized to burn size (0.8 ± 0.4 vs. 0.6 ± 0.4 days, $P < 0.05$), increased mortality (28% vs. 8%, $P < 0.05$), and longer duration of diarrhea (13 ± 16 vs. 4 ± 5 days, $P < 0.005$).

As shown in Figure 2, the longer the patients stayed in the ICU, the higher their risk of acquiring *C. difficile*, indicating that an association exists between *C. difficile* and length of ICU stay.

Because our case-control matching indicated differences in mortality, we conducted a survival log-rank analysis. Figure 3a shows survival probability in CDAD patients and controls. We found that CDAD patients in the non-matched population had lower probability of survival than non-CDAD patients, as seen by logistic regression (Figure 3b). This held true even in case-control propensity matching (Figure 3c-d). CDAD was associated with increased death, as shown by propensity-matched log-rank analyses.

Discussion

This study showed that CDAD is associated with greater duration of hospitalization, and time suffering from diarrhea, and increased mortality. *C. difficile* causes acute inflammation of the colon and can produce conditions ranging from diarrhea to fulminant pseudomembranous colitis.¹⁰ This is partly attributable to the release of toxins A and B into the lumen, which causes inflammation of the colon and subsequent diarrhea. Toxin A is an enterotoxin that leads to fluid shift, while toxin B is a cytotoxin. The two toxins synergistically induce cellular damage and vascular permeability changes, leading to cell death. Commonly reported symptoms of CDAD are abdominal pain, diarrhea, and fever. Patients also have leukocytosis. In this study, the symptoms reported were fever, abdominal distension, and leukocytosis. A literature review suggests that the variation in clinical manifestations of *C. difficile* infection is probably correlated with both the concentration of toxins in the patient and host factors such as the presence or absence of colonic receptors for these toxins. The varied presentation is also linked to the ability of the host immune system produce IgG in response to either of the disease toxins. Severely burned patients are susceptible to diarrhea secondary to a prolonged hospital stay, use of multiple antibiotics, a prolonged hypermetabolic state, and immune suppression.¹¹ Here, 289 out of 2,840 (10% incidence) patients experienced at least one bout of high stool output during hospitalization. Other pathophysiological changes thought to lead to diarrhea in burn patients are episodes of decreased mesenteric blood flow and the inability of the ileus or/and atonic bowel to tolerate large fluid loads presented by enteral feeding.

All patients in our ICU receive concomitant therapy with PPIs to prevent burn-related gastrointestinal ulceration or gastritis, which can further contribute to the occurrence of CDAD in burn patients. Theories posit that *C. difficile* spores are more likely to survive in a

less acidic stomach environment or that PPIs modulate toxin receptor function or toxin production in the gut. This hypothesis was not confirmed here. However, this may be attributable to the small number of CDAD patients studied. Interestingly, our case-cohort analysis revealed that the control group was exposed to fluoroquinolone treatment significantly more than the CDAD group. Pepin et al.¹² described fluoroquinolone use as a predominant risk factor for CDAD in a retrospectively studied cohort. Weiss responded in 2006,¹³ that every antibiotic can be the cause of CDAD. Thus we believe that our finding can show that fluoroquinolones alone might not necessarily be associated with a higher risk for CDAD. Further studies are needed to evaluate antibiotics associated risk factors in severely burned children.

Despite small patient numbers, we believe that our findings are valid, due to the vigorous analysis matching patients using propensity score analysis. Our study shows that treatment early after onset is important. It is not always easy to diagnose CDAD early in the severely burned patient, because antimicrobial therapy reduces the ability of the intestinal microflora to break down unabsorbed carbohydrates with resultant osmotic diarrhea. Differentiation between the two forms of diarrhea in severely burned patients depends on the clinical setting. All CDAD patients received oral metronidazole for 10 days or longer. Repeat stool examinations were conducted in patients with continuing diarrhea while receiving a therapy and were found to be negative for *C. difficile* toxins. No cross-contamination between patients or recurrences of CDAD were observed in the studied cohort.

In conclusion, CDAD was seen infrequently in severely burned pediatric patients and tended to respond well to treatment with metronidazole; however, this disease was associated with a high mortality. Our study population had no incidence of *C. difficile* colitis, which is often fatal. It is not entirely clear whether CDAD may be an indicator of more severe injury and/or disease severity. The finding that CDAD was associated with poorer survival in massively burned children underscores the need for greater attentiveness in evaluating and treating CDAD in this population. Early recognition of signs and symptoms of CDAD as well as testing for *C. difficile* toxins should be a priority so that appropriate therapy can be initiated early. The association of CDAD with higher mortality also highlights the importance of implementing isolation precautions to prevent further spread of the infection amongst patients and identifying risk factors associated with CDAD. However, additional investigations are needed in order to identify interventions that may improve survival.

Acknowledgements

We thank all the individuals who participated in this clinical trial. We also thank Dr. Kasie Cole for editing and proofreading this manuscript.

Sources of Financial Support. This study was supported by grants from the National Institute for Disabilities and Rehabilitation Research (H133A070026 and H133A70019 to D.N.H.), the National Institutes of Health (P50 GM060338, R01 GM056687, and T32 GM008256 to D.N.H.), Shriners Hospitals for Children (84080, 84309, 71008, 79141, and 8660 to D.N.H.), the Canadian Institutes of Health Research (No. 123336 to M.G.J.), CFI Leader's Opportunity Fund (Project No. 25407 NIH RO1 GM087285-01 to M.G.J.), and the Physicians' Services Incorporated Foundation—Health Research Grant Program. This work was also supported in part by a Clinical and Translational Science Award from NCATS (UL1TR001439).

Abbreviations

CDAD	<i>Clostridium difficile</i> -associated diarrhea
TBSA	Total body surface area
PPI	Proton pump inhibitor

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Fig 1.

Patient Selection. Cases of *C. difficile* were matched to comparison groups for case-control and case-cohort analyses, as described in methods. Two comparison groups were matched in a 1:4 ratio using logistic regression to calculate propensity scores. Propensity scores in the case-control study were calculated according to admission within 7 days post burn and days at occurrence. The case cohort study propensity scores were calculated according to percent TBSA burned, percent third-degree burn, inhalation injury, and admission within 7 days post burn. One case did not match to any controls and was excluded from the case-control study.

Fig 2.
Rate of Acquisition of *C. Difficile* as a function of hospital stay.

Figure 3a

Figure 3b

Figure 3c **Figure 3d** **Fig 3.**

Effect of *C. Difficile* on survival. Probability of survival to hospital discharge (a,c) and according to burn severity (b,d), before (a,b) ($n=288$) and after case-cohort matching (c,d) ($n=72$). Percent TBSA burned was an independent predictor of survival (b,d). The non-CDAD group is labeled “control group” and the CDAD group “C. difficile +”.

Table 1Characteristics of 18 burned children with *Clostridium difficile*-associated diarrhea.

Characteristic	Value
Median age, y	4
Sex, No. (%)	
Female	5 (28)
Male	13 (72)
Hispanic, No. (%)	12 (71)
Percent total body surface area burned, mean±SD	59±29
Percent third-degree burns, mean±SD	44±38
Type of burn, No. (%)	
Flame	14 (78)
Scald	4 (22)
Inhalation, No. (%)	10 (56)
Baux score, mean±SD	64±32
Post-burn day of diagnosis, Median (Q1, Q3)	11 (7, 21)
Antibiotic use during hospitalization within 9 weeks before	
Penicillins (± β -lactamase inhibitors)	14 (78)
Carbapenems	12 (67)
Fluoroquinolones (ciprofloxacin, levofloxacin)	8 (44)
Polypeptides	6 (33)
Other antibiotics (rifampin, linezolid,	6 (33)
Sulfonamides	5 (28)
Cephalosporins (first- and fourth-generation)*	3 (17)
Lactobacillus, No. (%)	4 (22)
No antibiotics, No. (%)	0 (0)

* No cases were administered second- or third-generation cephalosporins.

Table 2Characteristics of patients with *Clostridium difficile*-associated diarrhea and matched case controls.

Quality of 1:4 Matching	<i>C. Difficile</i> Patients (n=17)	Controls (n=68)	P Value
Age, y			0.15
Median	4	4	
Interquartile range	2–5	2–8	
Admitted within 7 days post burn, No. (%) *	15 (88)	60 (88)	1.00
Time to admission, mean±SD, days	5±9	4±4	0.37
Days at risk for <i>C. difficile</i> -associated diarrhea, mean±SD *	26±22	30±25	0.57
Propensity score, mean±SD *	0.07±0.03	0.08±0.03	0.48
Major burn, No. (%)	17 (100%)	68 (100%)	NA
Characteristic / Risk Factor			
No. of <i>C. difficile</i> assays within days at risk			0.38
Median	1	1	
Interquartile range	1–1	1–2	
Male, No. (%)	13 (76)	44 (65)	0.40
Hispanic, No. (%)	12 (71)	56 (82)	0.31
Flame burn, No. (%)	13 (76)	45 (66)	0.56
Percent total body surface area burned, mean±SD	60±29	51±19	0.14
Percent third-degree burns, mean±SD	46±38	36±28	0.23
Baux score, mean±SD	65±32	58±19	0.29
Inhalation, No. (%)	10 (59)	21 (31)	0.04
No. of classes of antibiotics received, mean±SD	4.8±2	5.4±2	0.16
Exposure to antibiotics, No. (%)			
Penicillins (± β-lactamase inhibitors)	13 (77)	39 (58)	0.26
Carbapenems	11 (65)	53 (79)	0.21
Fluoroquinolones	7 (41)	49 (73)	0.02
Metronidazole	6 (35)	13 (19)	0.19
Polypeptides	6 (35)	22 (33)	1.00
Sulfonamides	5 (29)	28 (42)	0.41
Cephalosporins	2 (12)	19 (28)	0.21
Other (i.e., Linezolid, Synercid, Rifampin)	6 (35)	32 (48)	0.42
Lactobacillus, No. (%)	3 (18)	18 (27)	0.54
Stress ulcer prophylaxis (Proton-pump inhibitors or Histamine H ₂ -blockers), No. (%)	17 (100)	67 (99)	1.00

* Logistic regression was used to calculate propensity scores based on exposure delimited by time to admission within 7 days post burn and number of days at risk. Matching was blindly performed at a 1:4 ratio according to the nearest matching propensity score. Quality of matching is shown.

Table 3

Comparison of clinical outcomes between patients with *Clostridium difficile*-associated diarrhea and matched cohort patients.

Quality of 1:4 Matching	<i>C. Difficile</i> Patients (n=18)	Controls (n=72)	P Value
Age, y			0.05
Median	4	6.5	
Interquartile range	2–5	3–13	
Male, No. (%)	13 (72)	57 (79)	0.54
Percent total body surface area burned, mean±SD *	59±29	58±22	0.89
Percent third-degree burns, mean±SD *	44±38	44±31	0.93
Inhalation, No. (%) *	10 (56)	34 (47)	0.60
Admitted within 7 days post burn, No. (%) *	15 (88)	59 (82)	1.00
Propensity score, mean±SD *	0.07±0.02	0.07±0.02	0.37
Baux score, mean±SD	64±32	66±22	0.73
Outcome			
Deaths, No. (%)	5 (28)	6 (8)	0.04
Length of ICU stay, mean±SD, days	48±36	37±33	0.24
Length of stay/% TBSA survivors, mean±SD, days/%	0.82±0.4	0.60±0.4	0.03
No. of days with stool output > 20 ml/g/day, mean±SD	34±28	25±24	0.18
Stool output during diarrhea (ml•kg ⁻¹ •min ⁻¹) mean±SD	31±9	28±11	0.39
No. of days of diarrhea and hypernatremia, mean±SD	8±13	5±10	0.22
Sodium level during episodes of hypernatremia, (mEq/L), mean±SD	150±4	150±3	0.86
No. of days of diarrhea and hyponatremia, mean±SD	10±11	10±11	0.99
Sodium level during episodes of hyponatremia, (mEq/L), mean±SD	130±6	132±2	0.07
No. of days of diarrhea and alkalosis, mean±SD	13±18	14±15	0.80
pH level during episodes of alkalosis, mean±SD	7.49±0.02	7.48±0.01	0.19
No. of days of diarrhea and acidosis, mean±SD	13±16	4±5	0.0002
pH level during episodes of acidosis, mean±SD	7.27±0.04	7.29±0.04	0.13

* Logistic regression was used to calculate propensity scores based on percent total body surface area (TBSA) burned, percent third-degree burns, inhalation injury, and admission within 7 days post burn. Matching was blindly performed at a 1:4 ratio according to the nearest matching propensity score. Quality of matching is shown.