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Clostridioides difficile infections complicating combat-injured patients from Iraq and Afghanistan

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Clostridioides difficile-associated diarrhea (CDAD) is the most frequently reported healthcare-associated illness in the United States, with an annual economic burden >$1 billion and up to 9% mortality, and critically ill trauma patients may be uniquely at risk.[1–4] Military trauma patients have multiple CDAD risk factors, including frequent broad-spectrum antimicrobial exposure, transient immunosuppression, and challenges related to infection control in the deployed environment and along the evacuation chain. We describe the epidemiology of wounded military personnel diagnosed with CDAD.

Methods

Wounded military personnel (June 2009 through February 2014) from the Trauma Infectious Disease Outcomes Study[5] with a diagnosis of confirmed (laboratory supported) or presumptive (diarrhea with treatment for CDAD without lab confirmation) CDAD were examined. Inclusion criteria were active-duty or Department of Defense beneficiaries, aged ≥18 years, injured during deployment, requiring medical evacuation to Germany followed by transfer to participating US military hospitals. Infections were defined as previously described.[5] CDAD diagnosis was based on a combination of clinical and laboratory findings suggesting CDAD and/or directed antimicrobial therapy against CDAD for ≥5 days.[5] CDAD severity was defined according to the 2017 guidelines using highest creatinine and white blood cell values on day of diagnosis.[6] The study was approved by the Institutional Review Board of the Uniformed Services University.

Results

Among 2,660 wounded military personnel, 23 patients with CDAD were identified (4 presumptive and 19 confirmed), with an incidence of 2.76 per 10,000 occupied bed days (OBD). Overall, 7 cases were confirmed by toxin enzyme immunoassay, 11 by polymerase chain reaction, and 1 by both methods. Patients were primarily young (median age, 24 years) men (96%) who sustained blast injuries (70%), resulting in critical injuries (median injury severity score [ISS], 38) (Table 1). Prior to CDAD diagnosis, patients were hospitalized a median of 12 days, and 17 (74%) had ≥1 infection, most commonly pneumonia (47%) and skin and soft-tissue infections (SSTIs, 47%). Severe CDAD was diagnosed in 8 (35%) and fulminant CDAD was diagnosed in 6 (26%) patients. Furthermore,

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19 patients (83%) were admitted to the intensive care unit (ICU) and 74% were intubated prior to or at the time of diagnosis.

Nearly all patients (96%) received antibiotics prior to CDAD diagnosis: 96% received first-generation cephalosporins, 87% received tetracyclines (largely doxycycline for malaria chemoprophylaxis), 70% received carbapenems, 57% received fluoroquinolones, and 22% received clindamycin. Comparatively, among 2,637 patients without CDAD, 91% received antimicrobials during their hospitalizations: 88% received tetracyclines, 86% received first-generation cephalosporins, 70% received carbapenems, 47 received fluoroquinolones, and 16% received clindamycin. Among CDAD patients, 87% and 57% were exposed to ≥3 and ≥5 antibiotic classes, respectively, with a median of 13 days of antibiotic exposure prior to CDAD diagnosis. During the study period, only Brooke Army Medical Center (6 CDAD patients) tracked CDAD rates, with concurrent annual incidences of 1.15 per 10,000 OBD in 2009, 0.78 in 2010, 1.9 in 2011, 2.7 in 2012, 4.7 in 2013, and 7.8 in 2014. Military hospitals in the National Capital Region only tracked incidences of healthcare-onset CDAD in 1 of the 2 admitting hospitals in 2013 and 2014, during which time the rates were 9.43 and 8.34 per 10,000 OBD, respectively.

Treatment included oral metronidazole alone in 15 patients, intravenous metronidazole alone in 2 patients, and combination of oral vancomycin, metronidazole, and intravenous metronidazole in 6 patients. No patients with CDAD died.

Table 1. Characteristics of Wounded Military Personnel with *Clostridioides difficile*-Associated Diarrhea (CDAD)

Patient Characteristics	Patients (N=23), No. (%)
Age, median y (IQR)	24 (23–31)
Injury severity score, median (IQR)	38 (26-47)
Mechanism of injury	
Blast	16 (69.6)
Gunshot wound	4 (17.4)
Other	3 (13.0)
Days hospitalized prior to diagnosis, median (IQR)	12 (9.5, 34)
ICU admission prior to or at CDAD diagnosis	19 (82.6)
Intubated prior to or at CDAD diagnosis	17 (73.9)
Prior diagnosis of ≥1 infections	17 (73.9)
Pneumonia	8 (34.8)
Skin and soft-tissue infection	8 (34.8)
Bloodstream infection	6 (26.1)
Sepsis	4 (17.4)
Osteomyelitis	2 (8.7)
CNS infection	2 (8.7)
Urinary tract infection	2 (8.7)
Intraabdominal infection	1 (4.3)
Tracheobronchitis	1 (4.3)
Antimicrobial exposure prior to CDAD diagnosis	22 (95.7)
First generation cephalosporin	22 (95.7)
Tetracycline	20 (87.0)
Vancomycin	17 (73.9)
Carbapenem	16 (69.6)
Fluoroquinolone	13 (56.5)
Clindamycin	5 (21.7)
Antimicrobial exposure by number of antibiotic classes prior to CDAD diagnosis	
≥1 class	22 (95.7)
≥3 classes	20 (87.0)
≥5 classes	13 (56.5)
Days of antibiotic exposure prior to CDAD, median (IQR)	13 (9.25–27.5)
Operating room visit prior to diagnosis	22 (95.6)
Intubated prior to CDAD diagnosis	17 (73.9)

Note. ICU, intensive care unit; IQR, interquartile range; CNS, central nervous system.

Discussion

Prior civilian trauma population studies demonstrated incidences of CDAD similar to nontrauma critically ill patients (1%–3% and 4%–5%, respectively) despite a lack of traditional risk factors.[3,4] Despite widespread antimicrobial use in our military trauma population, CDAD rates were low (0.86%; 2.76 per 10,000 OBD). A study of cumulative antibiotic exposure in hospitalized patients showed a median of 14 antibiotic days in CDAD patients,[7] similar to the median of 13 antibiotic days identified in our population. The same study identified a median of 3 antibiotic class exposures in the CDAD group, while our CDAD patients received a median of 6 antibiotic class exposures prior to diagnosis. More than half of patients were exposed to ≥5 antibiotic classes prior to CDAD diagnosis, which is consistent with literature suggesting higher CDAD risk with increased number of antibiotic class exposures.[7] We noted extensive tetracycline exposure in our population, largely driven by malaria prophylaxis. Although tetracyclines have demonstrated lower risk for CDAD than other antibiotics, given the high degree of broad antimicrobial class exposure, current data are insufficient to determine whether tetracycline exposure impacted our population.[8]

Similar to civilian trauma cohorts,[3,4] our CDAD patients were severely injured and were primarily admitted to the ICU, were intubated prior to diagnosis, and were diagnosed >1 week into their hospitalizations. This high injury severity is characteristic of the overall TIDOS population: 64.5% with blast injuries; 38% with ISS ≥25; 52% admitted to the ICU; 33% mechanically ventilated.[9] Among our CDAD patients, 74% were diagnosed with ≥1 preceding infection, and 34% of the overall TIDOS population had ≥1 infection, primarily SSTIs.[9]

Patients were primarily treated with metronidazole due to contemporary literature and guidelines during the study period.[2] Although CDAD was severe or fulminant in >50% of patients, there were no deaths. This finding differs dramatically from mortality rates in nontrauma patients (30%–80% in severe cases), but it is similar to that in civilian trauma studies and may result from our population being aged in their mid-20s and healthy prior to trauma.[3,4,10] Although our study largely involved penetrating trauma (compared to blunt trauma in civilian studies),[3,4] we were unable to evaluate certain CDAD risk factors (eg, gastric acid suppression, enteral feeding, and intraabdominal surgery) and complications (eg, toxic megacolon or colonic perforation). Further investigation is needed to determine whether penetrating and blunt trauma populations have distinct risk factors for CDAD.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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