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Clinical Outcomes

Outcomes in patients tested for *Clostridium difficile* toxins☆,☆☆

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ABSTRACT

Clostridium difficile testing is shifting from toxin detection to *C. difficile* detection. Yet, up to 60% of patients with *C. difficile* by culture test negative for toxins and it is unclear whether they are infected or carriers. We reviewed medical records for 7046 inpatients with a *C. difficile* toxin test from 2005 to 2009 to determine the duration of diarrhea and rate of complications and mortality among toxin-positive (toxin+) and toxin− patients. Overall, toxin− patients had less severe diarrhea, fewer diarrhea days, and lower mortality ($P < 0.001$, all comparisons) than toxin+ patients. One toxin− patient ($n = 1/6121$; 0.02%) was diagnosed with pseudomembranous colitis, but there were no complications such as megacolon or colectomy for fulminant CDI among toxin− patients. These data suggest that *C. difficile*–attributable complications are rare among patients testing negative for *C. difficile* toxins. More studies are needed to evaluate the clinical significance of *C. difficile* detection in toxin− patients.

1. Introduction

Clostridium difficile infection (CDI) is responsible for 25–30% of antibiotic-associated diarrhea in healthcare settings and nearly all cases of pseudomembranous colitis (PMC) and megacolon associated with antibiotics (Bartlett, 2002; Rupnik et al., 2009). It is estimated that 200,000 to 500,000 cases of CDI occur in acute care facilities in the United States each year affecting up to 1% of US hospital admissions (Campbell et al., 2009; Elixhauser and Jhung, 2008; Jarvis et al., 2009; McDonald et al., 2006). Yet, accurate diagnosis of CDI remains a significant barrier to treatment and the optimal test is unclear, despite numerous laboratory comparisons (Cohen et al., 2010; Dubberke et al., 2011; Kufelnicka and Kirn, 2011; Wilcox et al., 2010).

For decades, *C. difficile* toxin tests were accepted as an important laboratory adjunct in the diagnosis of CDI because toxins were believed to be responsible for the majority of clinical manifestations and toxin detection helped distinguish *C. difficile* carriage from CDI (Gerding et al., 1995; Viscidi et al., 1981). Since then, the essential role of *C. difficile* toxins in CDI pathogenesis has been confirmed and a relationship between toxin concentration and severity has been observed (Akerlund et al., 2006; Kuehne et al., 2010; Lyras et al., 2009; Rupnik et al., 2009; Ryder et al., 2010). Nonetheless, concern that patients with CDI may be missed by reliance on toxin tests has prompted a movement away from toxin testing towards methods that detect toxigenic *C. difficile* directly, such as polymerase chain reaction (PCR) and glutamate dehydrogenase (GDH) algorithms (Cohen et al., 2010; Eastwood et al., 2009; Gilligan, 2008; Kufelnicka and Kirn, 2011; Lemee et al., 2004; Peterson et al., 2007; Reller et al., 2007; Sharp and Gilligan, 2010; Sloan et al., 2008; Tenover et al., 2010; Wilcox et al., 2010). These tests are more sensitive for *C. difficile* in toxin− samples but may be less specific for CDI (Dubberke et al., 2011; Kufelnicka and Kirn, 2011; Wilcox et al., 2010). For example, if 20% of hospitalized patients are colonized with *C. difficile* (Cohen et al., 2010; Kyne et al., 2000; McFarland et al., 1989; Samore et al., 1994; Viscidi et al., 1981) and most nosocomial diarrhea is unrelated to CDI (Bartlett, 2002; Garey et al., 2006; McFarland, 1995; Yadav et al., 2009), it seems likely that some patients with diarrhea and *C. difficile* are carriers with diarrhea due to other causes (Kufelnicka and Kirn, 2011; Wilcox et al., 2010). Thus, toxin tests may miss occasional patients with CDI, while direct tests for *C. difficile* may result in overdiagnosis and over-treatment. This dilemma points to a critical unmet need to understand the natural history of toxin− patients to inform the *C. difficile* test debate.

To address this issue, we reviewed the electronic medical records (EMR) of a large cohort of hospitalized patients tested for *C. difficile* toxins during a period when other *C. difficile* tests were not performed. Our goals were to compare the frequency of *C. difficile*–attributable complications and duration of symptoms among toxin− and toxin+ patients as an indication of the number of CDI patients missed by routine toxin tests. The frequency of CDI treatment was also evaluated

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in both groups with the assumption that empiric treatment in toxin− patients provides an indication of the level of clinical suspicion for CDI.

2. Materials and methods

2.1. 2005–2009 dataset

Records from patients ≥1 year old admitted to the UC Davis Medical Center (UCDMC) from January 1, 2005, to December 31, 2009, with a current procedural test code for *C. difficile* toxin test were analyzed retrospectively. Based on the toxin test results, patients and admissions were classified as *C. difficile* toxin+ or toxin− including tests performed up to 90 days prior to admission and 90 days after discharge. Repeat toxin test results were included. Administrative data, medical, and laboratory records were used to identify patients with PMC diagnosed by endoscopy or histopathology or a CDI-attributable complication (e.g., megacolon, colectomy for fulminant colitis). Specifically, all records with an *ICD-9-CM* code for rigid or flexible sigmoidoscopy or colonoscopy (45.23, 45.24, 45.25, 48.23, 48.24), partial or total colectomy (45.79, 45.80), or megacolon (564.7), and all pathology reports with a diagnosis of PMC were individually reviewed. Preexisting patient comorbidities were enumerated using software available from the Agency for Healthcare Research and Quality (AHRQ) based on the method of Elixhauser et al. (1998) (AHRQ, 2011), and crude mortality 6 months after discharge was assessed from UCDMC records.

2.2. 2009 subset

For admissions between January 1 and December 31, 2009, the duration and severity of diarrheal symptoms and the frequency of CDI-directed treatment among toxin+ and toxin− patients were also assessed. For each admission, stool counts recorded in the EMR were separated into 16-day test episodes beginning 2 days prior to the date of sample collection for the toxin test. Episodes were analyzed for the number of diarrhea days defined as ≥3 stools per 24-h period and classified as severe if any day had ≥10 stools recorded. When stool output was recorded as a volume, we divided the volume by 200 mL to estimate the number of bowel movements per day. Patients (episodes) with a peripheral blood white blood cell count ≥15K cells/mm^3 within ±3 days of the *C. difficile* sample collection date were classified as having a leukocytosis. Inpatient pharmacy data for metronidazole and oral vancomycin dispensing were matched with *C. difficile* episodes and test dates. For toxin− episodes, metronidazole treatment initiated within the 72-h period, including the day of stool sample collection ±1 day, was classified by manual chart review into 1 of 3 categories: 1) empiric therapy for an enteric process or CDI; 2) unrelated to enteric process or CDI; or 3) undetermined. Metronidazole started outside this period was excluded.

2.3. Laboratory

C. difficile toxin testing was performed on fresh, diarrheal stool samples using the Premier *C. difficile* toxins A & B test (Meridian Bioscience, Inc.; Cincinnati, OH, USA) following the manufacturer's instructions. Other tests such as toxigenic culture or PCR were not performed during the study period. Formed stool samples were tested on physician request.

2.4. Statistical analysis

The analysis was limited to the first toxin+ admission or diarrheal episode in the case of toxin+ patients and to the first admission or episode in toxin− patients during the study period. The frequencies of categorical variables, such as sex or the proportion of patients with ≥2 comorbidities, a CDI complication, death, or leukocytosis, etc., were compared between groups using the chi-square or Fisher's exact tests. Nonparametric continuous variables (e.g., age, hospital days, intensive care unit [ICU] days, diarrhea days, antibiotic days) were compared between groups using the Mann–Whitney *U* test.

3. Results

From 2005 to 2009, 7046 hospitalized patients ≥1 year old were tested for *C. difficile* toxins during the study period. Of these, 925 (13.1%) tested positive for *C. difficile* toxins including 914 (98.8%) new-onset CDI cases and 11 (1.2%) recurrences; 6121 (86.9%) patients tested negative for toxins, although it is likely that some of these patients had *C. difficile* not detected by toxin testing (Lemee et al., 2004; Peterson et al., 2007; Reller et al., 2007; Sloan et al., 2008). The characteristics and outcomes of these patients are summarized in Table 1. Overall, toxin+ and toxin− patients had a similar number of preexisting comorbidities and differed statistically but not practically in their age and sex composition. However, toxin+ patients were more frequently admitted to an ICU as part of their hospitalization, had longer lengths of hospital and ICU stay, and had a higher mortality rate than toxin− patients ($P < 0.001$, all comparisons). Five toxin+ patients had histologically confirmed PMC. One toxin− patient was found to have PMC at autopsy, but this was a secondary diagnosis and the patient's death was attributed to hepatorenal syndrome as a complication of cirrhosis and urosepsis. Two toxin+ patients developed a complication of CDI (megacolon, $n = 1$; fulminant CDI requiring colectomy, $n = 1$). No CDI complications were documented among toxin− patients. Taken together, 7 (0.8%) of 925 toxin+ patients had biopsy-confirmed PMC or a complication of CDI versus 1 (0.02%) of 6121 toxin− patients ($P < 0.001$) (Table 1).

During 2009, 1671 inpatients had 1 or more episodes of diarrhea accompanied by a *C. difficile* toxin test. With the use of the first positive episode of toxin+ patients and the first episode of toxin− patients, 202 (10.7%) toxin+ diarrheal episodes and 1469 (89.3%) toxin− diarrheal episodes were analyzed. Toxin+ episodes had more days with diarrhea than toxin− episodes (3.3 versus 2.0 days; $P < 0.001$) and a greater proportion of episodes with severe diarrhea

Table 1
Complications and mortality for toxin+ and toxin− patients (2005–2009).[a]

	Toxin+	Toxin−	*P*
Patients (*n*)	925	6121	
Age (median)	56 (Range: 1-101)	54 (Range: 1-100)	<0.05
Female (*n*)	416 (45.0%)	2973 (48.6%)	<0.05
≥2 Comorbidities (*n*)	108 (11.7%)	647 (10.6%)	0.44
Hospital length of stay (days, median)	17 (Range: 1-586)	10 (Range: 1-748)	<0.001
ICU stay (*n*)	482 (52.1%)	2462 (40.2%)	<0.001
ICU days (median)	12 (Range: 0-204)	8 (Range: 0-303)	<0.001
≥3 *C. difficile* tests/ admission (*n*)	308 (33.3%)	1028 (16.8%)	<0.001
CDI discharge code, 008.45 (*n*)[b]	775 (83.8%)	68 (1.1%)	<0.001
Biopsy-confirmed PMC or CDI-attributable complication (e.g., megacolon, colectomy) (*n*)[c,d]	7 (0.8%)	1 (0.02%)	<0.001
Death (all causes, 6 months) (*n*)	125 (13.5%)	556 (9.1%)	<0.001

[a] Analysis limited to the first admission with ≥1 *C. difficile* test during the study period.
[b] *ICD-9-CM* code for *C. difficile* infection.
[c] Combined cases identified by review of patients with *ICD-9-CM* codes for rigid or flexible sigmoidoscopy or colonoscopy (45.23, 45.24, 45.25, 48.23, 48.24), partial or total colectomy (45.79, 45.80), or megacolon (564.7), or pathologic diagnosis of pseudomembranous colitis.
[d] Toxin+: PMC ($n = 5$), toxic megacolon ($n = 1$), colectomy for fulminant CDI ($n = 1$); toxin−: PMC ($n = 1$).