ORIGINAL ARTICLE

Reducing the risk of severe complications among patients with *Clostridium difficile* infection

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**BACKGROUND:** The incidence and severity of *Clostridium difficile* infections are increasing, and there is a need to optimize the prevention of complicated disease.

**OBJECTIVE:** To identify modifiable processes of care associated with an altered risk of *C. difficile* complications.

**METHODS:** A retrospective cohort study (with prospective case ascertainment) of all *C. difficile* infections during 2007/2008 at a tertiary care hospital was conducted.

**RESULTS:** Severe complications were frequent (occurring in 97 of 365 [27%] *C. difficile* episodes), with rapid onset (median three days postdiagnosis). On multivariable analysis, nonmodifiable predictors of complications included recent antimicrobial infection (OR 2.67), confusion (OR 2.01), hypotension (OR 0.97 per increased mmHg) and elevated white blood cell count (OR 1.04 per 10^9 cells/L). Protection from complications was associated with initial use of vancomycin (OR 0.24); harm was associated with ongoing use of exacerbating antibiotics (OR 3.02).

**CONCLUSION:** *C. difficile* infections often occur early in the disease course and are associated with high complication rates. Clinical factors that predicted a higher risk of complications included confusion, hypotension and leucocytosis. The most effective ways to improve outcomes for patients with *C. difficile* colitis are consideration of vancomycin as first-line treatment for moderate to severe cases, and the avoidance of unnecessary antibiotics.

**Key Words:** *Clostridium difficile*; Complications; Metronidazole; Risk factors; Vancomycin

**METHODS**

**Study cohort**

A retrospective cohort study (with prospective case ascertainment) was conducted at Sunnybrook Health Sciences Centre (SHSC) – a large, 700-bed academic health sciences centre in Toronto, Ontario. All consecutive cases of *C. difficile* infection were prospectively identified by the Department of Infection Prevention and Control between January 1, 2007, and December 31, 2008. As per standard provincial guidelines, the case definition required laboratory confirmation of a positive toxin assay, together with diarrhea or visualization of pseudomembranes on sigmoidoscopy, colonoscopy or histopathology (13). Diarrhea was defined as two or more loose/watery bowel movements in a 24 h period that was unusual or different for the patient, and with no other recognized etiology (13). During the period examined in the present study, stool testing at SHSC was performed using enzyme immunoassay (EIA) for *C. difficile* toxins A and B (TECHLAB, Inverness Medical, United Kingdom). Patients were excluded from analysis only in the rare event that they were enrolled in an investigational study of a novel *C. difficile* therapy (n=3), or if their medical chart was unavailable for abstraction after three attempts (n=5).

**RESULTS:**

Serious complications were frequent (occurring in 97 of 365 [27%] episodes of *C. difficile* infection) and were associated with high complication rates. Prediction of complications included recent infection (OR 2.67), confusion (OR 2.01), hypotension (OR 0.97 per increased mmHg) and elevated white blood cell count (OR 1.04 per 10^9 cells/L). Protection from complications was associated with initial use of vancomycin (OR 0.24); harm was associated with ongoing use of exacerbating antibiotics (OR 3.02).

**CONCLUSION:** The infections to *C. difficile* se produisent souvent au début de l’évolution de la maladie et s’associent à de forts taux de complications. Les facteurs cliniques qui présagent un risque plus élevé de complications incluent la confusion, l’hypotension et la leucocytose. Les meilleurs moyens d’améliorer les issues des patients atteints de colite à *C. difficile* consistent à envisager un traitement de première ligne à la vancomycine dans les cas modérés à graves et à éviter les antibiotiques inutiles.
The primary outcome measure was a composite of severe complications including severe hypokalemia (potassium level lower than 2.5 mM), toxic megacolon (colonic distension of greater than 7 cm or cecal dis- tension of greater than 12 cm), bowel perforation, lower gastrointestinal bleeding requiring blood transfusion, intensive care unit transfer or death before completion of treatment for an episode of \textit{C. difficile} infection (4). In secondary sensitivity analyses, the outcome definition was varied to exclude the least severe events (eg, hypokalemia) or least preventable complications (eg, outcome events occurring before positive diagnostic test results). Outcome events were adjudicated by retrospective chart review conducted by two of the study authors.

Nonmodifiable predictors (baseline characteristics and clinical presentation)

Extensive data regarding baseline patient characteristics were collected. Demographic data included age, sex and place of residence. The source of infection was determined prospectively and defined as nosocomial if the onset occurred more than 72 h after hospital admission, or was related to a previous admission to a health care facility within the previous eight weeks (13). Comorbidities of interest included the following: cardiac disease, lung disease, liver disease, renal disease, neurological disease, inflammatory bowel disease, malignancy, diabetes mellitus, HIV/AIDS, preceding surgery during the current admission and gastrointestinal tube feeding. The acuity of the clinical presentation during the first 48 h of illness was assessed by measurement of maximum heart rate, minimum systolic blood pressure (mmHg), maximum number of stools per day, presence of blood in stool, abdominal pain, confusion, maximum white blood cell count ($\times 10^9$cells/L), maximum creatinine level (mM) and minimum albumin level (g/L).

Modifiable predictors related to processes of care

Emphasis was placed on modifiable care processes relevant to the diagnosis and treatment of patients with \textit{C. difficile} infection. Important diagnostic measures included the duration of symptoms before diagnosis (days), laboratory stool assay turnaround time (same day or longer), negative stool EIA results preceding a positive stool EIA result (as a measure of impact of imperfect test sensitivity), and the use of abdominal x-ray testing or abdominal computed tomography scans. Treatment measures included the following: delays in treatment beyond 24 h from the time of the positive \textit{C. difficile} test result, any use of metronidazole, any use of oral/rectal vancomycin, inclusion of vancomycin in the initial therapeutic regimen, adjunctive use of probiotics (Saccharomyces boulardii or Lactobacillus preparations), use of potentially exacerbating antibiotic treatments after \textit{C. difficile} diagnosis and the use of antimotility agents (diphenoxylate or loperamide).

Prevention of \textit{C. difficile} complications

Univariate analysis was undertaken to compare each modifiable and nonmodifiable predictor variable among \textit{C. difficile} episodes with and without severe acute complications. The $\chi^2$ test was used to assess differences for binary predictors, while Wilcoxon rank-sum tests were used to examine differences for continuous variables. Multivariable logistic regression was the primary analysis used to assess the incremental impact of modifiable and nonmodifiable predictors on the risk of severe complications during an episode of \textit{C. difficile} infection. Assuming a baseline complication rate of 22%, a power of 85% (alpha = 0.05) was estimated to detect a 15% increased risk of complications associated with each predictor (4,14). Generalized estimating equations were used to account for the fact that some patients experienced multiple \textit{C. difficile} episodes (15). Variable reduction was accomplished by backward selection after including significant predictors on univariate analysis (ie, $P<0.1$) as well as prespecified inclusion of initial vancomycin therapy. Laboratory tests (albumin, imaging tests (x-ray and computed tomography scans) and endoscopy were not performed in the majority of patients and, therefore, could not be included in multivariable models. To assess the robustness of the results, secondary multivariable analysis was also repeated with variations in the composite outcome (as described above). All analyses were performed using SAS version 9.1 (SAS Institute, USA). The study was approved by the research ethics board of the SHSC.

RESULTS

General characteristics of the cohort

The cohort included 305 individual patients who experienced a total of 365 episodes of \textit{C. difficile} infection. Almost all infections were associated with diarrhea (n=360 [99%]), and almost all were diagnosed on the basis of a positive stool EIA performed at the SHSC (n=361 [99%]). The majority of cases were nosocomial (n=335 [91%]), attributed to the current hospital admission (n=291 [80%]), a previous SHSC admission (n=26 [7%]) or a previous admission to another health care facility (n=16 [4%]). A majority of infections (n=30 [8%]) were community acquired. Most patients were elderly (mean [± SD] 71±16 years of age), with at least one underlying illness (n=327 [90%]).

Risk and timing of severe complications

Severe complications occurred in 97 of 365 (27%) episodes of \textit{C. difficile} infection. Table 1 summarizes the rates of each individual complication. These complications occurred rapidly (median three days post-diagnosis, interquartile range one to nine days), and 15 (16%) preceded the positive stool assay (Figure 1).

Individual nonmodifiable predictors of \textit{C. difficile} complications

Different baseline characteristics were demonstrated between patients who experienced uncomplicated and complicated episodes of \textit{C. difficile}
infection (Table 2). Severe complications were more common among older patients, and those with underlying cardiac or neurological disease. Clinical presentation also differed between uncomplicated and complicated cases (Table 3). A greater risk of severe complications was associated with tachycardia, hypotension, confusion, recurrent episodes of infection, leukocytosis, elevated creatinine levels and hypoalbuminemia. Results were similar when recurrent episodes of C. difficile infection were excluded from the analysis (data not shown).

**Modifiable predictors of C. difficile complications**

Diagnosis of C. difficile infection was delayed beyond four days of diarrhea symptoms in 20% of patients; however, there was no difference in diarrhea duration between uncomplicated and complicated episodes (Table 4). Laboratory results were not available on the same calendar day as specimen collection for 93 (25%) episodes, with no differences between uncomplicated and complicated episodes. An initial stool assay was negative before the positive result in 59 (16%) episodes, which was associated with a delay in diagnosis (7±8 days versus 3±5 days; P<0.0001), but not with an increased risk of complications. Abdominal x-rays and computed tomography scans were more frequently obtained for patients with complicated compared with uncomplicated disease; however, the proportion of abnormal imaging findings was similar in both groups.

Initiation of effective antibiotic therapy (metronidazole or vancomycin) was delayed more than one calendar day from the positive stool assay result for 20% of episodes; however, the likelihood of delayed therapy was similar between complicated and uncomplicated episodes of C. difficile infection. Clinical presentation also differed between uncomplicated and complicated cases (Table 3). A greater risk of severe complications was associated with tachycardia, hypotension, confusion, recurrent episodes of infection, leukocytosis, elevated creatinine levels and hypoalbuminemia. Results were similar when recurrent episodes of C. difficile infection were excluded from the analysis (data not shown).

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cases (Table 4). Almost all C difficile infections were treated with metronidazole (92%), and only a minority of cases were treated with vancomycin at some point in their course (28%). There was a trend toward greater use of vancomycin in the initial treatment regimen for uncomplicated versus complicated episodes (8.3% versus 4.1%; P=0.18). The use of probiotics and antimotility agents was similar between complicated and uncomplicated episodes, but the continued use of exacerabating antibiotics after diagnosis was far more common among patients who experienced complicated episodes of infection (78% versus 54%; P=0.0001).

**Multivariable analysis: Independent predictors of severe C difficile complications**

Multivariable analysis yielded six independent predictors of severe C difficile complications, including four nonmodifiable factors and two potentially modifiable factors (Table 5). Nonmodifiable factors included repeat infection (OR 2.67 [95% CI 1.23 to 5.80]), confusion (OR 2.01 [95% CI 1.05 to 3.83], systolic hypotension (OR 0.97 [95% CI 0.95 to 0.98] per increased mmHg) and elevated white blood cell count (OR 1.04 [95% CI 1.02 to 1.07] per 10^9 cells/L). Inclusion of vancomycin in the initial therapeutic regimen was protective (OR 0.24 [95% CI 0.08 to 0.71]), while the use of exacerabating antibiotics was hazardous (OR 3.02 [95% CI 1.56 to 5.86]). These findings were unchanged in sensitivity analyses, which excluded the least severe outcome (hypokalemia) and the least preventable outcomes (those developing before sensitivity analyses, which excluded the least severe outcome (hypokalemia) and the least preventable outcomes (those developing before

**DISCUSSION**

Our study highlights the gravity of C difficile infection among hospitalized patients, as well as prospects to improve their outcomes. Severe complications were common among patients with C difficile infections, occurring in more than one in four episodes, and corroborated the findings of a recent national surveillance study (4). These complications occurred rapidly, often even before confirmatory test results, thereby emphasizing the importance of infection prevention and control measures to prevent new cases of infection (16). However, recent literature suggests that high-performing institutions are distinguished not only by their prevention of iatrogenic illnesses, but also by their capacity to detect and manage them (17). Our study highlights the gravity of C difficile infection among patients who experienced complicated episodes of infection (78% versus 54%; P=0.0001).

**TABLE 5**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse (versus initial) episode</td>
<td>2.67</td>
<td>1.23–5.80</td>
</tr>
<tr>
<td>Confusion</td>
<td>2.01</td>
<td>1.05–3.83</td>
</tr>
<tr>
<td>Systolic blood pressure, per increased mmHg</td>
<td>0.97</td>
<td>0.95–0.98</td>
</tr>
<tr>
<td>Elevated WBC, per 10^9 cells/L</td>
<td>1.04</td>
<td>1.02–1.07</td>
</tr>
<tr>
<td>Vancomycin as initial treatment</td>
<td>0.24</td>
<td>0.08–0.71</td>
</tr>
<tr>
<td>Other exacerabating antibiotics</td>
<td>3.02</td>
<td>1.56–5.86</td>
</tr>
</tbody>
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WBC White blood cell count

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REFERENCES