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Outcome of metronidazole therapy for *Clostridium difficile* disease and correlation with a scoring system☆

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Summary *Objectives:* To determine the response rate of *Clostridium difficile* disease (CDD) to treatment with metronidazole and assess a scoring system to predict response to treatment with metronidazole when applied at the time of CDD diagnosis.
Methods: Retrospective review of patients with CDD who received primary treatment with metronidazole. We defined success as diarrhea resolution within 6 days of therapy. A CDD score was defined prospectively using variables suggested to correlate with disease severity.
Results: Among 102 evaluable patients, 72 had a successful response (70.6%). Twenty-one of the remaining 30 patients eventually responded to metronidazole, but required longer treatment, leaving 9 'true failures'. The mean CDD score was higher among true failures (2.89 ± 1.4) than among all metronidazole responders (0.77 ± 1.0) ($p < .0001$). The score was greater than 2 in 67% of true failures and 2 or less in 94% of metronidazole responders. Leukocytosis and abnormal CT scan findings were individual factors associated with a higher risk of metronidazole failure.
Conclusions: Only 71% of CDD patients responded to metronidazole within 6 days, but the overall response rate was 91%. A CDD score greater than 2 was associated with metronidazole failure in 6 of 9 true failures. The CDD score will require prospective validation.
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Introduction

Metronidazole has been considered by many clinicians as the drug of choice for *Clostridium difficile* disease (CDD),[1] based on a 94–95% success rate in early clinical trials[2–5] and the concern for vancomycin use facilitating resistance in *Enterococcus* or *Staphylococcus*.[1] Recent evidence suggests that a favorable response to metronidazole is not as predictable as previously reported.[6–10] Factors associated with treatment failures include low albumin, intensive care unit admission,[10,11] or a higher severity of illness or comorbidity burden.[12–14] Other reports suggest that new epidemic *C. difficile* strains are associated with increased severity of disease and complications.[6,7] It has been suggested that severe CDD cases should initially be treated with vancomycin, but there are no accepted criteria for defining CDD severity.[1,11]

We conducted this study to determine whether the clinical response rate of CDD to treatment with metronidazole in our hospital is different from the previously reported rate of 94–95% and prospectively defined a clinical scoring system and assessed its utility in predicting metronidazole treatment success or failure when applied at the time of CDD diagnosis.

Material and methods

Hines VA Hospital is a 472-bed tertiary care referral center with 117 acute medical–surgical inpatient beds, a 68 inpatient-bed Spinal Cord Injury Unit, and a 199-bed Residential Long Term Care Facility. Patients admitted to Hines from January 2003 to September 2004 and who developed CDD were identified by a review of consecutive stool toxin assay results from the Clinical Microbiology Laboratory records. Patients with a 1 positive stool assay for *C. difficile* toxin A (VIDAS® *C. difficile* toxin A II., BioMérieux, Inc., Durham, NC, USA) were included if they met the following criteria: (1) any documentation by the treating physician of ''diarrhea'' or ''loose stools'' in their clinical record, (2) no other recognized etiology of diarrhea, (3) no prior episode of CDD, and (4) treatment with metronidazole for at least 5 days. This 5-day rule was used to allow comparison with previously reported prospective studies.[2,3] In cases with more than 1 episode of CDD, we analyzed only the first episode. Patients who were diagnosed at the Long Term Care Facility, transferred from another institution with a diagnosis of CDD, or diagnosed as outpatients, were excluded due to the lack of documentation regarding the dates of onset and resolution of diarrhea and of initiation and discontinuation of metronidazole treatment.

Administrative data collected for each case included demographics, admission and discharge dates, ICD-9-based primary diagnosis and comorbidities, bed transfers, and 30-day all-cause mortality after diagnosis of CDD. Medical information included the date of the first positive stool toxin assay, primary admitting illnesses, and comorbidities; use of metronidazole and other systemic antibiotics (including agents, doses and dates of administration); and time to resolution of diarrhea, time to first recurrence if present, and laboratory data. Other procedures (e.g., computed tomography [CT] scan, colonoscopy, and sigmoidoscopy), and complications of CDD, such as toxic megacolon, ascites, colectomy, and shock were also recorded. The severity of the primary illness responsible for hospital admission and the comorbidities were measured by the Horn's index[13,15] and the Charlson's score,[16] respectively.

To develop and assess a scoring system to predict metronidazole treatment outcome, we hypothesized that treatment failure would correlate with CDD severity. We then constructed an empiric CDD score that included variables previously suggested in the literature to correlate with a higher disease severity: fever, ileus, hypotension, leukocytosis, and specific CT abnormalities (Table 1).[6,17–22] Fever was defined as a temperature $\geq$38.0 °C. The diagnosis of ileus was based on a clinical or radiologic diagnosis as recorded in the chart. Hypotension was defined as any systolic blood pressure reading $<$100 mmHg, and leukocytosis as any white blood cell count value $\geq$15,000 cells/mm^3. CT scan findings included colonic wall thickening, colonic dilatation, and ascites (otherwise unexplained). The individual CDD score variables were recorded based on measurements obtained as close as possible to the positive toxin assay and initiation of treatment (within 3 days of positive CDD toxin assay). All variables were assigned a priori weight of 1 except for leukocytosis and CT scan findings which were weighted as 1 or 2, depending on the level of leukocytosis or the number of CT findings (Table 1). The CDD score could range from 0 to 7. Variables that could potentially reflect either underlying host factors or CDD (e.g., albumin and creatinine) were analyzed separately. We defined recurrences as a new episode of *C. difficile* toxin positive diarrhea within 60 days of complete resolution of the previous episode of diarrhea.

Response to therapy

We classified the response to treatment of CDD as a success if diarrhea and other symptoms resolved within 6 days of starting metronidazole.[2,3,10] Successful responses were further categorized as documented successes (DS) or presumptive cures (PC). DS included those episodes where

Table 1 *Clostridium difficile* disease score

Variable	Points
Fever (38.0 °C)	1
Ileus[a]	1
Systolic blood pressure $<$ 100 mmHg[b]	1
Leukocytosis	
WBC $<$ 15,000/mm^3	0
WBC $\geq$ 15,000/mm^3, $<$30,000/mm^3	1
WBC $>$ 30,000/mm^3	2
CT scan findings (thickened colonic wall, colonic dilatation, ascites)	
No findings	0
1 Finding	1
$\geq$2 Findings	2

[a] Ileus diagnosed by clinical or radiographic findings.
[b] Any single reading within 3 days of CDD diagnosis.