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High Horn's index score predicts poor outcomes in patients with *Clostridium difficile* infection

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SUMMARY

Several variables have been proposed to predict the prognosis of patients with *Clostridium difficile* infection (CDI), but a clinically useful tool to stratify resource utilization has not been determined. Horn's index, a severity score based on underlying clinical illness, reliably predicts patients at high risk of CDI. The purpose of this study was to assess the use of Horn's index to stratify patients with CDI at high risk of poor clinical and economic outcomes. Hospitalized patients diagnosed with CDI were followed prospectively for three months. Horn's index scores were calculated for each patient on the day of the positive toxin test for *C. difficile*, and used to stratify differences in outcome variables (length of hospital stay, mortality and hospital costs). Eighty-five CDI patients (50% male, 64% Caucasian) were recruited. Discharge mortality was 0% for patients with Horn's index scores of 1 or 2, 5% for those with a score of 3, and 50% for those with a score of 4 ($P < 0.001$). Three-month mortality was 0%, 5%, 17% and 60% for patients with Horn's index scores of 1, 2, 3 and 4, respectively ($P = 0.0004$). Median three-month hospital costs were $8585, $12,670, $29,077 and $68,708 for patients with Horn's index scores of 1, 2, 3 and 4, respectively ($P < 0.001$). Patients with Horn's index scores of 3 or 4 had a significantly longer hospital stay [mean 33.4 (standard deviation, SD 33.3) days] than patients with scores of 1 or 2 [mean 15.1 (SD 16.2) days, $P = 0.001$]. This study found Horn's index to be a simple and useful method for identifying CDI patients at high risk of poor clinical and economic outcomes.

Introduction

Clostridium difficile is the most common definable cause of nosocomial diarrhoea in hospitalized patients.[1,2] Clinical presentations of *C. difficile* infection (CDI) include asymptomatic carriage, antibiotic-associated colitis without pseudomembrane formation, pseudomembranous colitis and fulminant colitis. The number of cases of CDI tripled in North America and Europe between 1996 (31 per 100,000 population) and 2005 (84 per 100,000 population).[3] The increasing disease burden of CDI has been attributed to several factors, including increased use of broad-spectrum antibiotics, an ageing population, increasing comorbidities and the emergence of the hypervirulent NAP1/BI/027 strain of *C. difficile* in North America and Europe.[4] This epidemic strain is associated with increased mortality, high recurrence rates and poor response to currently available antibiotics. The increasing disease burden is accompanied by an increasing financial burden on healthcare systems.[5,6] According to recent conservative estimates, direct annual costs of CDI management are nearly $3.4 billion for an estimated 246,139 cases of CDI per year.[6–8] The attributable costs of CDI among non-surgical patients alone were estimated to range between $1.9 million and $2.8 million per year at a single tertiary care hospital.

The changing epidemiology, coupled with the increasing incidence, mortality and treatment failure rates, underscore the need to look for alternative treatment and prevention strategies, hence the importance of identifying high-risk patients. Several clinical factors

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(e.g. old age, hospital stay), and immunological and inflammatory responses, have been studied as risk factors for primary and recurrent CDI, but a clinically useful tool to stratify the risk of poor outcomes in patients with CDI has not been determined.[9]

Horn's index ranks a patient on a four-level index of disease severity, and has been shown to reliably predict outcomes in general.[10] A qualified clinician rates the severity of the underlying disease, giving the patient a score of 1 (single mild illness), 2 (more severe illness but uncomplicated recovery expected), 3 (major illness or complications or multiple conditions requiring treatment) or 4 (catastrophic illness that may lead to death). Using a modified version of Horn's index, McFarland *et al.* found that age and extremely severe underlying disease were strong independent risk factors for *C. difficile* diarrhoea.[11] Subsequently, a high Horn's index score was shown to be major risk factor for both primary and recurrent CDI.[12,13] However, it has not been determined if Horn's index can also stratify CDI patients at high risk of poor outcomes. The premise of this study was that assessment of Horn's index on the day of the positive toxin test for *C. difficile* would be a simple clinical measure that would take into account the severity of CDI along with the underlying comorbid conditions of the patient. It was hypothesized that assessment of Horn's index on the day of the positive toxin test in patients with CDI would be predictive of clinical and economic outcomes. Identification of high-risk patients at the time of *C. difficile* test positivity could be helpful in predicting resource requirements, and could potentially be used as a stratification measure for interventions designed to decrease mortality and morbidity in patients with CDI.

Table I
Demographic, past medical history and hospitalization characteristics of the study subjects

	Horn's index score		*P*-value
	1 or 2	3 or 4	
	N (%)	*N* (%)	
Demographics			
Sex			
Male	9 (27)	35 (67)	0.0003
Female	24 (73)	17 (33)	
Age, years (mean ± SD)	64 ± 19	65 ± 15	0.81
Ethnicity			0.13
Caucasian	18 (55)	37 (71)	
Hispanic	3 (9)	7 (13.5)	
African American	11 (33)	8 (15.5)	
Asian	1 (3)	0 (0)	
Past medical history			
Congestive heart failure	6 (18)	17 (33)	0.14
Chronic obstructive pulmonary disease	6 (18)	11 (21)	0.74
Diabetes	12 (36)	22 (42)	0.58
Chronic renal failure requiring haemodialysis	0 (0)	10 (19)	0.0073
Myocardial infarction	3 (9)	11 (21)	0.14
Obesity	3 (9)	6 (11)	0.72
Hospitalization history[a]			
Severe leukocytosis	23 (70)	26 (50)	0.14
Abnormal albumin	4 (12)	14 (27)	0.23
Intensive care unit	2 (6)	14 (27)	0.053
Treated with oral vancomycin	9 (27)	6 (12)	0.064

SD, standard deviation.
[a] Assessed on the day of the positive toxin test for *Clostridium difficile*.

Methods

This prospective observational study was carried out at St Luke's Episcopal Hospital at the Texas Medical Center, Houston, TX, USA. Consecutive patients hospitalized between March 2007 and May 2008 with a positive toxin test for *C. difficile* were screened for enrolment. Patients were eligible to participate in the study if they were diagnosed with CDI, defined as diarrhoea that was not attributed to any other enteric pathogen and was associated with a positive stool toxin test for *C. difficile* using the cell cytotoxicity assay against toxin B.[14] Patients with active chronic diarrhoea (e.g. Crohn's disease) were excluded. The study was approved by the institutional review board at St. Luke's Episcopal Hospital. Informed consent was obtained from all patients or their healthcare proxies.

At study entry, age, sex, ethnicity and information on known risk factors for CDI were recorded. Other variables recorded included past medical history (congestive heart failure, chronic obstructive pulmonary disease, diabetes, chronic renal failure requiring haemodialysis, myocardial infarction and obesity) and hospitalization variables collected on the day of the positive toxin test for *C. difficile* [severe leukocytosis (>15,000 cells/mL), abnormal albumin (<2.5 g/dL), hospitalized in the intensive care unit and primary treatment with oral vancomycin] (Table I). Modified Horn's index was assessed as described by McFarland *et al.* and Hu *et al.*[11,13] Horn's index score was assigned on the day of the positive toxin test by study investigators, and the evaluation required <15 min to complete for each patient. Evaluation included a review of the patient's medical chart and a clinical examination. Patients were followed-up for a period of three months; daily during their stay in hospital, weekly during the first month after discharge, and monthly for the next two months.

Definitions of outcomes

The main outcomes of interest were mortality (in-hospital and 30 days following diagnosis of CDI) and three-month hospital costs. Cost data were obtained from the hospital accounting database, and represent total direct hospital costs including daily ward and intensive care unit (ICU) charges, diagnostic tests, physician consultations, ancillary health professional consultations and pharmacy costs. Recurrent CDI was defined as a new episode of diarrhoea beginning at least two days after resolution of the initial episode and after discontinuation of *C. difficile* antibiotics, and lasting for at least 48 h. Refractory CDI was defined as continued diarrhoea after six days of CDI antibiotic therapy.

Statistical analysis

Severity of disease was dichotomized as Horn's index scores of 1 or 2 and Horn's index scores of 3 or 4. Associations between Horn's index scores and outcomes were examined using Chi-squared test or two-tailed Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was considered to be significant.

Results

Patient demographics and CDI presentation

Eighty-five patients with a mean age of 65 [standard deviation (SD) 16] years were recruited. Forty-four (52%) patients were male and 55 (65%) were Caucasian. Thirty-nine (46%) patients were diagnosed with CDI within 48 h of admission. The most common comorbid conditions were congestive heart failure (n = 23/27%), chronic obstructive pulmonary disease (n = 17/20%), diabetes (n = 34/40%), chronic renal disease requiring haemodialysis (n = 10/12%), previous myocardial infarction (n = 14/17%) and obesity (11%). Twelve (14%) patients had a history of CDI. On the day of the positive toxin test for *C. difficile*, 49 of 85 (58%) patients had an abnormal white blood cell count, 18 (21%) had an abnormal albumin result and 16 (19%) were in the ICU. Metronidazole was