SUPPLEMENT ARTICLE

Renal Failure and Leukocytosis Are Predictors of a Complicated Course of *Clostridium difficile* Infection if Measured on Day of Diagnosis

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Nonsevere *Clostridium difficile* infection (CDI) and severe CDI, which carries a higher risk than nonsevere CDI for treatment failure and CDI recurrence, are difficult to distinguish at the time of diagnosis. To investigate the prognostic value of 3 markers of severe CDI suggested by recent guidelines (fever, leukocytosis, and renal failure), we used the database of 2 randomized controlled trials, which contained information for 1105 patients with CDI. Leukocytosis (risk ratio [RR], 2.29; 95% confidence interval [CI], 1.63–3.21) and renal failure (RR, 2.52; 95% CI, 1.82–3.50) were associated with treatment failure. Fever, although associated with treatment failure (RR, 2.45; 95% CI, 1.07–5.61), was rare. Renal failure was the only significant predictor of recurrence (RR, 1.45; 95% CI, 1.05–2.02). Different timing of measurements of leukocyte count and serum creatinine level around the CDI diagnosis led to a different severity classification in many cases. In conclusion, both leukocytosis and renal failure are useful predictors, although timing of measurement is important.

Clostridium difficile infection (CDI) has become an increasing problem in many hospitals in the Western world during the past decade. *C. difficile* causes diarrhea and colitis, with a tendency to recur after initially successful antimicrobial therapy. Furthermore, gut inflammation may be so severe that antimicrobial therapy is not effective; in such cases, complications such as hypotension, perforation, and toxic megacolon may develop. Several risk factors for CDI have been identified, of which the use of antibiotics is the most important. Predicting which patients are at risk for developing complications or recurrences can guide the choice and duration of therapy. In 2009, a prediction rule for recurrences, incorporating age, comorbid conditions, and the necessity to continue inciting antibiotic therapy, was published [1]. This rule was derived from and was validated in 2 cohorts of 44 and 64 patients, respectively. The relatively small sample sizes challenge the credibility of this rule. Several risk factors for complications of CDI and prediction rules based on these factors have been described, but unfortunately, none of these prediction rules have been validated [2–6].

The choice of an appropriate end point for a prediction rule for complicated and/or recurrent CDI has been problematic. The clinical judgment of whether to attribute end points such as CDI-related mortality and intensive care unit admission may be highly subjective, especially for elderly patients, who are often admitted with severe illness and usually have significant comorbid conditions. End points concerning the resolution and recurrence of diarrhea need a precise definition of diarrhea and quantitative measurement of stool volume and frequency, which may be difficult to obtain.

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Furthermore, the parameters included in a prediction rule should be objective, routinely measured in clinical practice, and available at the moment the rule is applied (ie, when CDI is diagnosed).

A recent guideline by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America recommends that age, peak leukocyte count, and peak serum creatinine level be taken into account as potential indicators of a complicated course of CDI when treatment is started [7]. The European Society for Clinical Microbiology and Infectious Diseases has issued a guidance document for the treatment of CDI that also lists qualitative and quantitative symptoms, signs, laboratory parameters, and radiological findings that may reflect more severe disease with associated higher risk for complications and recurrences [8]. Three quantitative parameters for diagnosing severe colitis were included: body temperature >38.5°C, leukocyte count $>15 \times 10^9$/L, and serum creatinine level >50% above baseline; however, these cutoffs have not been confirmed prospectively.

In the present study, we sought to investigate the value of 3 quantitative severity criteria in predicting the failure of antimicrobial therapy and the recurrence of CDI after initially successful treatment. Furthermore, we aimed to investigate whether leukocyte count and serum creatinine level fluctuate early in the course of a CDI episode and therefore whether the timing of their measurements can influence whether severity criteria are met. For our analyses, we used the database from 2 large randomized clinical trials that used a strict objective definition of diarrhea and the database of a prospective single-center cohort study that recorded sequential leukocyte counts and serum creatinine levels around the date of CDI diagnosis.

METHODS

Databases

The database from 2 randomized controlled phase III trials comparing vancomycin with fidaxomicin for the treatment of CDI was used to assess the predictive value of fever, leukocyte count, and serum creatinine level [9, 10]. Patients were recruited in the United States, Canada, and Europe (ClinicalTrials.gov registry number NCT00314951, April 2006–July 2008, United States and Canada; and ClinicalTrials.gov registry number NCT00468728, April 2007–November 2009, United States, Belgium, Canada, France, Germany, Italy, Spain, Sweden, and United Kingdom). Patients with CDI, defined on the basis of diarrhea (>3 unformed bowel movements [UBMs] per day) and a positive stool toxin test for *C. difficile*, were randomly assigned to receive 125 mg of vancomycin 4 times daily or 200 mg of fidaxomicin twice daily for 10 days. The numbers and times of UBMs were recorded during treatment and for 2 days after an end-of-therapy visit. For patients with rectal collection devices, volume was converted to number of UBMs by dividing the volume by 60 mL and rounding up to the nearest whole number. At the end-of-therapy visit, an investigator assessed the success of therapy. Clinical failure was defined as the persistence of diarrhea, the need for additional therapy for CDI, or both on the basis of the opinion of the investigator [10]. Recurrence of CDI (determined by use of the same criteria as for enrollment [ie, >3 UBMs per 24 hours and a positive stool toxin test result]) was assessed during the mean follow-up duration (±SD) of 28 ± 2 days after completion of therapy. At enrollment, temperature, leukocyte count, and serum creatinine level were collected.

To assess whether the timing of laboratory measurements could influence their prognostic value, we used the database of a prospective cohort study performed at Leeds Teaching Hospital in 2007. In this database, 104 consecutive adult inpatients with CDI (defined on the basis of the presence of unformed stool and a positive *C. difficile* toxin test result) were included. On days −3 to +3 relative to day 0 (the day the diarrheal sample was collected), leukocyte count and serum creatinine level were recorded. Data from a minimum of 2 leukocyte counts and creatinine levels on different days were required for patients to be included in the analyses.

In both analyses, we defined fever as a core body temperature >38.5°C and leukocytosis as a leukocyte count $>15 \times 10^9$ leukocytes/L. Because the pre-CDI serum creatinine level was not known for each patient, we substituted the 50% creatinine level increase with a fixed value of the creatinine level >133 μmol/L (>1.5 mg/dL). This served as a proxy for renal failure.

Analyses

The intention-to-treat population that received at least 1 dose of study medication was used for the analysis. Distributions of the continuous variables of temperature, leukocyte count, and creatinine level were compared for patients with and patients without clinical treatment failure and recurrence. Nonnormally distributed variables were compared with the Mann-Whitney *U* test. Proportions were compared with the χ^2 test. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for the associations of fever, leukocytosis, and renal failure with the outcome parameters. Kaplan-Meier survival curves were constructed to investigate the association of fever, leukocytosis, and renal failure with the time to resolution of diarrhea (expressed in hours from the first dose of fidaxomicin or vancomycin). The log-rank test was used to test the difference between the survival curves. Cox regression was used to calculate hazard ratios (HRs) with 95% CIs. Receiver operating characteristic curves were constructed to assess the validity of the cutoffs used to define categorical variables. Variability of leukocyte counts and serum creatinine levels were compared

within patients and expressed in absolute differences. All analyses were carried out in SPSS for Windows software, version 17.0 (SPSS, Chicago, IL).

RESULTS

There were 1105 patients with CDI in the clinical trial database. Patients treated with vancomycin (n = 566) or fidaxomicin (n = 539) had similar median values for temperature, leukocyte count, and serum creatinine level and were evenly distributed across the groups with respect to dichotomized continuous variables (data not shown). Fever was rare; only 1.2% of patients (13 of 1102) had a temperature >38.5°C. The median treatment duration was 11 days for each group. Overall, 143 patients (13%) experienced clinical treatment failure at the end of treatment. Of the 962 patients who were cured after treatment, 194 (20%) experienced recurrence a mean (±SD) of 28 ± 2 days after treatment.

The median leukocyte count and creatinine level were significantly higher in patients with clinical treatment failure; temperature distributions in patients with and those without treatment failure were almost identical. In addition, dichotomous categories of fever, leukocytosis, and renal failure all showed significant correlation with treatment failure (Table 1). The median creatinine level was significantly higher in patients with recurrence, and this parameter was the only significant predictor of recurrence (Table 2). Different cutoffs for the continuous variables of temperature, leukocyte count, and creatinine level, assessed by receiver operating characteristics, did not lead to higher relative risks and therefore better performance in the prediction of clinical treatment failure or recurrent CDI.

The probability of resolution of diarrhea within 10 days of treatment was slightly lower in patients with renal failure, compared with patients without renal failure (HR, 0.83; 95% CI, .68–1.02; Figure 1). Neither fever (HR, 1.08; 95% CI, .61–1.91) nor leukocytosis (HR, 1.02; 95% CI, .84–1.24) was associated with a lower probability of resolution of diarrhea. Although creatinine level distributions were similar between patients treated with fidaxomicin and those treated with vancomycin, we repeated the analysis of renal failure as a predictor of resolution of diarrhea stratified according to treatment group and found similar results (vancomycin: HR, 0.80 [95% CI, .61–1.05]; fidaxomicin: HR, 0.88 [95% CI, .66–1.19]). Because recurrences occurred less often in patients treated with fidaxomicin, the CI is widest in that group.

Clinical treatment failure rates were similar in the fidaxomicin and vancomycin treatment groups regardless of clinical status, using the 3 severity factors. Recurrence was significantly more frequent following vancomycin treatment, compared with fidaxomicin treatment. In patients without renal failure, 93 of 402 patients (23.1%) cured by vancomycin therapy had a recurrence, whereas only 56 of 403 (13.9%) experienced a recurrence after successful fidaxomicin treatment ($P < .001$). In patients with renal failure at baseline, fidaxomicin therapy was associated with a 60% reduction in the frequency of recurrences (8 of 54 [14.8%]) relative to vancomycin (24 of 65 [36.9%]; $P = .007$). Likewise, in patients categorized as having leukocytosis or severe CDI, the incidence of recurrence was more than double for patients cured with vancomycin, compared with those treated successfully with fidaxomicin ($P < .01$ for each comparison).

Because leukocytosis and renal failure at the time of diagnosis were shown to be the strongest predictors, we investigated the stability of these parameters during a 6-day interval around diagnosis. In the population from the database of Leeds Teaching Hospital, the highest mean leukocyte count (13.4×10^9 leukocytes/L) was found on the day of CDI diagnosis. Within the interval from 3 days before to 3 days after the diagnosis of CDI, the mean difference between the highest and lowest leukocyte counts was 6.4×10^9 leukocytes/L. Twenty of 86 patients (23.3%) had a minimum to maximum leukocyte count range $>10 \times 10^9$ leukocytes/L, and 33 (38.4%)

Table 1. Determinants of Clinical Treatment Failure Among Patients With *Clostridium difficile* Infection

Variable	Median Value	IQR	P[a]
Continuous, outcome			
Temperature (°C)			
Failure	36.8	36.4–37.2	.180
Cure	36.7	36.4–37.1	
Leukocyte count ($\times 10^9$ leukocytes/L)			
Failure	10.5	6.8–17.4	.002
Cure	8.9	6.5–12.1	
Creatinine level (μmol/L)[b]			
Failure	80	62–150	.005
Cure	71	62–97	
Categorical, cutoff	**Failure[c]**	**RR[d]**	**95% CI**
Fever, temperature			
>38.5°C	4/13	2.45	1.07–5.61
≤38.5°C	137/1089		
Leukocytosis, leukocyte level			
$>15 \times 10^9$ leukocytes/L	38/153	2.29	1.63–3.21
$\leq 15 \times 10^9$ leukocytes/L	90/829		
Renal failure, creatinine level			
≥133 μmol/L[b]	41/160	2.52	1.82–3.50
<133 μmol/L[b]	91/896		

Abbreviations: CI, confidence interval; IQR, interquartile range; RR, risk ratio.

[a] Comparison between patients with clinical treatment failure and those with clinical cure.

[b] Creatinine conversion: 1 μmol/L is equal to 0.0113 mg/dL. Therefore, 133 μmol/L is equal to 1.50 mg/dL.

[c] Data are no. of patients with failure/overall no.

[d] For the association with failure.

Table 2. Determinants of *Clostridium difficile* Infection Recurrence

Variable	Median Value	IQR	P^a
Continuous, outcome			
Temperature (°C)			
No recurrence	36.7	36.4–37.1	.827
Recurrence	36.7	36.4–37.0	
Leukocyte count ($\times 10^9$ leukocytes/L)			
No recurrence	8.8	6.5–12.1	.276
Recurrence	9.1	6.6–12.8	
Creatinine level (μmol/L)[b]			
No recurrence	71	62–97	.008
Recurrence	80	62–115	
Categorical, cutoff	Recurrence[c]	RR[d]	95% CI
Fever, temperature			
>38.5°C	1/9	0.55	.09–3.51
≤38.5°C	192/952		
Leukocytosis, leukocyte level			
$>15 \times 10^9$ leukocytes/L	22/115	1.00	.67–1.50
$\leq 15 \times 10^9$ leukocytes/L	141/739		
Renal failure, creatinine level			
≥133 μmol/L[b]	32/119	1.45	1.05–2.02
<133 μmol/L[b]	149/805		

Abbreviations: CI, confidence interval; IQR, interquartile range; RR, risk ratio.

[a] Comparison between patients with recurrence and those without recurrence.

[b] Creatinine conversion: 1 μmol/L is equal to 0.0113 mg/dL. Therefore, 133 μmol/L is equal to 1.50 mg/dL.

[c] Data are no. of patients with recurrence/overall no.

[d] For the association with recurrence.

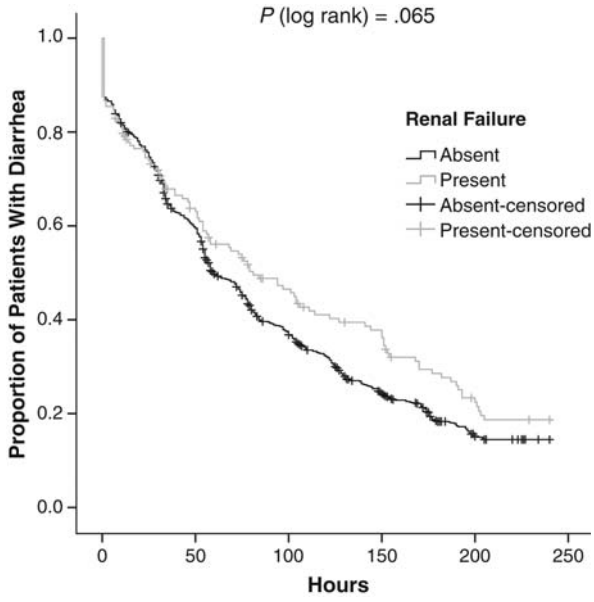

Figure 1. Kaplan-Meier analysis of time to resolution of diarrhea for patients with and without renal failure. The hazard ratio was 0.83 (95% confidence interval, .68–1.02).

patients had a minimum to maximum leukocyte count range that included the cutoff of 15×10^9 leukocytes/L; therefore, a difference in timing of a single blood sample around diagnosis could have led to a different severity classification. The mean serum creatinine concentration was 147 μmol/L on the day of diagnosis. The mean minimum to maximum range in serum creatinine values was 38.7 μmol/L. Nineteen of 93 patients (20.4%) had a minimum to maximum range in creatinine levels that included the cutoff of 133 μmol/L, which could have led to a different classification in the case of different timing.

DISCUSSION

Leukocytosis and renal failure were significant predictors of failure of CDI treatment. Only renal failure showed a trend toward longer duration of diarrhea during treatment and was correlated significantly with recurrence after successful treatment. Both leukocyte count and serum creatinine level were highly variable around diagnosis. Fever was found to be too infrequent in our study to be a useful predictor, but its associated relative risk was significant.

In previous studies, leukocytosis and renal failure were also associated with complications and recurrence of CDI [3, 11–13]. Therefore, both parameters could be suitable for evaluation in a prediction model. However, because of the variable nature of these values around the time of CDI diagnosis, a strict definition is needed before incorporating these parameters in a prediction rule. Early or late diagnosis could influence leukocyte count and serum creatinine level. Fever appeared not to be a useful predictor of failure of CDI treatment. This was also shown by a small study in 2007 [14].

Both fever and leukocytosis are thought to reflect more severe inflammation of the bowel wall. However, fever was too rare in our patient population to be of use as a predictor. Renal failure may reflect loss of effective circulating volume due either to dehydration because of diarrhea or to shock in the context of a systemic inflammatory response. Unfortunately, the predictive value of these parameters may decrease because of underlying illnesses and comorbid conditions. Renal failure was present in 14% of clinical patients and was the only significant predictor of recurrence, and it was the only parameter associated, albeit nonsignificantly, with a longer time to resolution of diarrhea. Thus, creatinine level may be a good predictor, also because of its relatively greater stability around the time of CDI diagnosis in comparison to leukocytosis.

Strengths of this study are the large number of patients with CDI in the database with a well-described definition of

diarrhea and a consistent measure of UBMs. One limitation is that other potential predictors of severe CDI, such as age, serum albumin level, or use of concomitant antibiotics, were not included in this analysis. Therefore, we were not able to develop a complete risk score. Another limitation is the absence of a baseline creatinine level for each patient, precluding us from distinguishing between chronic and acute renal failure.

The results of our study suggest that both leukocytosis and renal failure predict clinical treatment failure, whereas only renal failure is a predictor of recurrence after therapy. However, these predictors are highly dependent on the timing of their determination, hampering their use in clinical practice. We need better and more closely defined predictors to construct a reliable prediction score for complicated and recurrent CDI that is applicable in clinical practice.

Notes

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