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"Outcomes in community–acquired *clostridium difficile* infection"

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SUMMARY

Background—Community-acquired *Clostridium difficile* infection (CA-CDI) is an increasingly appreciated condition. It is being described in populations lacking traditional predisposing factors that have been previously considered at low-risk for this infection. As most studies of CDI are hospital-based, outcomes in these patients are not well known.

Aim—To examine outcomes and their predictors in patients with CA-CDI.

Methods—A sub-group analysis of a population-based epidemiological study of CDI in Olmsted County, Minnesota from 1991-2005 was performed. Data regarding outcomes, including severity, treatment response, need for hospitalization and recurrence were analyzed.

Results—Of 157 CA-CDI cases, the median age was 50 years and 75.3% were female. Among all CA-CDI cases, 40% required hospitalization, 20% had severe and 4.4% had severe-complicated infection, 20% had treatment failure and 28% had recurrent CDI. Patients who required hospitalization were significantly older (64 vs 44 years, $p<0.001$), more likely to have severe disease (33.3% vs 11.7%, $p=0.001$), and had higher mean Charlson comorbidity index scores (2.06 vs 0.84, $p=0.001$). They had similar treatment failure and recurrence rates as patients who did not require hospitalization.

Conclusions—CA-CDI can be associated with complications and poor outcomes, including hospitalization and severe CDI. As the incidence of CA-CDI increases, clinicians should be aware of risk factors (increasing age, comorbid conditions and disease severity) that predict the need for hospitalization and complications in patients with CA-CDI.

Keywords

Clostridium difficile infection; community-acquired; outcomes; predictors of hospitalization

INTRODUCTION

Clostridium difficile infection (CDI) has been traditionally recognized as a common cause of diarrhoea acquired in healthcare settings. Several hospital-based studies have previously

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demonstrated that CDI in hospitalized patients has been associated with adverse outcomes and increased mortality [1-4]. More recently, CDI is an increasingly recognized cause of diarrhoea in the community, especially in younger patients who were previously thought to be at low-risk of developing CDI, as they lack traditional risk factors including hospitalization and antibiotic exposure [2, 5-8]. The factors responsible for the emergence of CDI in the community are not clear, but could be related to emergence of novel risk factors, the epidemic *C. difficile* strain, food and water contamination or an increase in the proportion of asymptomatic carriers in the community leading to an increase in person-to-person transmission [5, 9-11]. The epidemiology of community-acquired CDI (CA-CDI) has been previously examined [2, 7, 12, 13], but outcomes such as need for hospitalization, development of severe and severe complicated infection, treatment failure and recurrence have not been extensively studied. Furthermore, predictors of these outcomes have not been previously determined. These outcomes have important implications for individual patients and health-care utilization and costs.

In this study, we assessed the likelihood and predictors of adverse outcomes in a population-based cohort of patients with CA-CDI.

MATERIALS AND METHODS

Study population

This study is a sub-group analysis of a recently completed epidemiological study of CDI occurring in residents of Olmsted County, MN from 1991 to 2005 [2]. Cases were identified using the resources of the Rochester Epidemiology Project (REP) [14, 15]. The REP database was searched for CDI as a microbiologic or clinical diagnosis (both inpatient and outpatient), and also for the ICD-9 code for CDI (008.45). Medical records from all sources of care available to Olmsted County residents are linked and accessible through the REP. A central diagnostic index maintains records from all outpatient visits, emergency room visits, hospitalizations, nursing home visits, surgical procedures, autopsy examinations, and death certificates for all residents since 1908. The REP allows investigators to follow subjects through their outpatient and hospitalization contacts across all local medical facilities, regardless of where the care was delivered and of insurance status.

All records of patients who had provided permission for their medical records to be used in research were reviewed. Clinical notes, laboratory results, endoscopy and histopathology reports were reviewed to confirm diagnoses. Records were reviewed to identify separate cases for individual patients, and determine acquisition modality (community vs. hospital). The overall epidemiology of this cohort has been reported previously [2]. Comorbid conditions for all patients were assessed by calculating the Charlson Comorbidity index [16]. The Charlson Comorbidity index is comprised of 19 comorbid conditions in 4 categories, and each category has a weighted-score based on the adjusted risk of one and ten-year mortality [16]. A higher Charlson score reflects a more severe comorbidity burden and an increased likelihood of one and ten-year mortality. Antibiotic exposure was defined as the use of oral or parenteral antibiotics in 90 days preceding CDI diagnosis. Acid-suppressing medication use was defined as the concomitant use of either a PPI or a H2-receptor blocker at the time of CDI diagnosis. The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved the study.

Case Definitions

Based on recent recommendations [17, 18], “definite” CDI was defined as ≥ 3 loose stools in 24 hours with a positive *C. difficile* stool toxin assay (which was being performed by enzyme immunoassay during the study period) or the presence of pseudomembranous colitis

on endoscopy or histology. Infection was defined as community-acquired if symptom onset occurred in the community or within 48 hours of admission to a hospital, provided symptom onset was more than 12 weeks after the last discharge from a hospital. Indeterminate infection was defined as symptom onset between 4 and 12 weeks after hospital dismissal and an a-priori decision was made to include these patients as community-acquired (n=20).

Recurrent CDI was defined if the diagnostic criteria for CDI were met within 8 weeks of initial diagnosis after documented symptom resolution [17, 18]. In accordance with the Infectious Diseases society of America guidelines, severe disease was defined by a white blood cell count ≥ 15,000 / mm^3 or a serum creatinine rise of ≥ 50% from baseline [18]. CDI was classified as 'severe complicated' if the infection was associated with hypotension, sepsis, ileus, toxic megacolon, perforation, need for ICU admission, surgery for a CDI-related complication (e.g. megacolon, perforation, refractory colitis), or death [18].

Statistical analysis

Statistical analysis was performed using JMP version 9.0.1 (SAS Institute Inc.). Descriptive analyses were performed for demographics, and all other clinical variables. For continuous variables, t-test was used for calculation of P-value and 95% confidence intervals when appropriate. For binary variables, chi-square test of independence was used and an alpha error rate was set at 0.05. The univariate associations of demographic and clinical characteristics with outcomes from CA-CDI were assessed via contingency tables analyses (chi square test). Multiple logistic regression models were used to evaluate the association of outcomes from CA-CDI with risk factors including age, sex, Charlson comorbidity index [16], prior antibiotic exposure and disease severity. Results are reported as medan (range), mean (± standard deviation), or as odd's ratio (95% confidence interval).

RESULTS

Patient characteristics

Using the resources of the REP, 385 definite cases of CDI in Olmsted County residents from 1991-2005 were identified [2]. Of these cases, 157 (41%) were CA-CDI, 192 (50%) were hospital-acquired and the remaining 36 (9%) occurred in residents of long-term care facilities such as nursing homes.

Community-acquired *C. difficile* infection

The median age of patients with CA-CDI was 50 years (range 1-102 years), and 76% were female. Of these patients, 13.3% were children (age <18 years), 14.7% were young adults (age 18 – 35 years), 40.7% were between age 36 and 65 years and 31.2% were elderly (age >= 65 years).

Need for hospitalization—Amongst all CA-CDI, 40% required hospitalization for CDI. These patients were significantly older, had higher Charlson Comorbidity index scores, and were less likely to have prior antibiotic exposure than those treated as outpatients (Table 1). Among CA-CDI patients, 33.3% of hospitalized patients had severe CDI compared with 11.7% of those treated as an outpatient (p=0.001). There were no differences in sex, recent gastrointestinal endoscopy procedures, acid suppression medication use, initial treatment for CDI, treatment failure or risk of recurrence amongst those hospitalized for CA-CDI compared to those managed as an outpatient (Table 1).

In a multivariate logistic regression model including age (in decades), sex, Charlson Comorbidity index, prior antibiotic exposure and disease severity, only sex did not predict the need for hospitalization in patients with community-acquired CDI (Table 2). Patients

who were hospitalized were less likely to be exposed to antibiotics before CDI, after adjusting for other factors (Table 2).

Severe Infection—Of the 157 patients with CA-CDI, 32 (20.4%) patients had severe CDI. Patients with severe infection were older (median age 69.5 years) than those with mild-moderate infection (median age 46 years). In univariate analyses, patients with severe CA-CDI had no differences in sex, prior antibiotic exposure, Charlson Comorbidity index, recent gastrointestinal endoscopy procedures, acid suppressing medication use, initial treatment, treatment failure or recurrence compared to patients with mild-moderate CDI (Table 3).

Severe complicated infection occurred in 7 (4%) of all CA-CDI. These patients were significantly older (median age 80 years versus 49 years, p=0.006) and had higher Charlson Comorbidity (5.77 versus 1.13, p<0.0001) than patients who had uncomplicated infection. There was no significant association between the risk of severe complicated infection and sex, prior antibiotic exposure, recent gastrointestinal endoscopy procedures, initial treatment, treatment failure or recurrent infection.

Treatment response and recurrence—Metronidazole was used as initial treatment in 133 (84.7%) patients and vancomycin in 15 (9.6%), and rifaximin in two patients. No antibiotic treatment was given in seven (4.5%). Of the 150 patients who were treated, 30 (20%) had non-response or intolerable side effects and were classified as treatment failures. In univariate analyses, CA-CDI patients with treatment failure were significantly older (median age 68 years versus 49 years, p=0.008), but had similar sex, prior antibiotic exposure, Charlson comorbidity index, recent gastrointestinal endoscopy procedure, severity, initial treatment and recurrence, compared to patients who did not have treatment failure. There were no differences in treatment failure in patients who received metronidazole or vancomycin as the initial treatment (21.8% versus 6.8%, p=0.12).

Recurrent infection occurred in 44 (28%) patients. In univariate analyses, patients with recurrent CA-CDI were similar to patients who had no recurrence including initial treatment, age, sex, Charlson Comorbidity index, prior antibiotic exposure, recent gastrointestinal endoscopy procedure, severity, initial treatment and treatment failure compared to those who had no recurrence.

DISCUSSION

In this population based cohort, CA-CDI occurred in 41% of all patients with CDI [2]. Among those with CA-CDI, 40% required hospitalization, 20% had severe and 4.4% had severe-complicated infection, 20% had treatment failure and 28% had recurrent CDI. Increasing age was a predictor of need for hospitalization, severe and severe complicated infection, and treatment failure, but not recurrence. Higher Charlson Comorbidity index scores predicted the need for hospitalization and severe-complicated infection, but not other outcomes.

The majority of CDI epidemiological data are derived from hospital-based reports and administrative databases [19-21]. There have been relatively few studies that have described the epidemiology and characteristics of CA-CDI [2, 5, 7, 12, 22-24]; in addition, outcomes in these patients have not been extensively studied. CA-CDI has been reported in populations previously considered to be at low-risk, including children and young adults [5]. A recent epidemiological study from the United Kingdom showed that almost all CA-CDI cases occurred in patients less than 65 years of age [12]. In contrast, in our cohort, almost one-third of patients with CA-CDI were elderly (age ≥ 65 years), similar to findings in another investigation where almost one-half of patients with CA-CDI were elderly [13]. These findings suggest that CA-CDI occurs among all age groups in the community. Increasing

age has been previously associated with both an increased risk of CDI [25] and with worse outcomes, including higher mortality [21]. Although CA-CDI has been characterized as generally a mild illness, 20% of our patients developed severe infection and 4.4% had severe-complicated infection. Increasing age and higher Charlson Comorbidity scores predicted likelihood of these outcomes.

Similar to a previous study [13], 40% of patients with CA-CDI in our cohort required hospitalization for management of CDI. Patients who required hospitalization were older, had higher comorbidity scores and a higher incidence of severe infection than those who were treated in the community. The need for hospitalization has tremendous impact on health-care costs and patient outcomes. Hospitalization inadvertently exposes patients to other risks and avoidable complications including venous thromboses and other nosocomial infections. Therefore, patients with CA-CDI who are older or who have higher comorbidity burden, as well as those who meet the current definition of severe infection (based on white blood cell count or rising creatinine) should be monitored closely and managed more aggressively in the community in order to prevent poor outcomes.

An interesting observation in our study was that patients who required hospitalization for CA-CDI were less likely to be exposed to antibiotics than those treated in the community. Although these patients were older and had more comorbidities than patients who were treated in the community, the decreased exposure to antibiotics persisted even after controlling for these confounders. Thus, the explanation for this observation is not clear, but other studies of CA-CDI have reported a lack of antibiotic exposure in many patients [12, 13]. For example, in a case-control study of CA-CDI, antibiotic exposure was not present in 52% of patients in the 4 week time period prior to CDI onset [7]. These results suggest other undefined risk factors for CDI in the community, such as *C. difficile* carriage in animals [26, 27] and retail meat products [28, 29]. Moreover, it has been hypothesized that increased *C. difficile* carriage in outpatients could contribute to the risk of CA-CDI in community dwellers without antibiotic exposure [9, 10].

In summary, a significant proportion of CDI in our cohort occurred in the community, possibly due to the presence of emerging newer risk factors or increasing asymptomatic carriage in the community. Although, CDI in the community could be considered benign, older patients with CA-CDI, especially those with higher comorbidity burden, are more likely to have adverse outcomes and require hospitalization for CDI.

The major strength of our study is that data were collected over 15 years in a stable population. The resources of the REP permitted identification of all cases of CDI in county residents and access to all the medical record information in each case. Because the study was population-based, we were able to capture information on clinical characteristics and outcomes in all patients with CDI, including community dwellers.

Potential limitations of the study include its retrospective nature and some missing data such as laboratory tests and lack of *C. difficile* strain information, which was not available from our laboratory during the time of the study.

CONCLUSIONS

A substantial proportion of patients with community-acquired CDI required hospitalization; they were older and more likely to have severe disease than those who could be treated in the community, but had similar rates of treatment failure and recurrence. Those hospitalized for CA-CDI were less likely to have received prior antibiotic exposure, suggesting that other undefined risk factors are associated with outcomes in community-acquired CDI. Given the burden of CA-CDI, clinicians should be aware of risk factors (increasing age, comorbidities

and disease severity) that predict need for hospitalization and other complications, and which might justify more aggressive medical therapy and monitoring. Future prospective studies are needed to evaluate outcomes in patients with CA-CDI.

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Table 1

Comparison of clinical features and outcomes among patients hospitalized versus not hospitalized for management of community-acquired *Clostridium difficile* infection

	Hospitalized for management of CDI (n=63)	Not-hospitalized (n=94)	p-value
Age (years), median (range)	64 (1-102)	44 (1- 86)	<0.0001
Female, n (%)	50 (79.4%)	69 (73.4%)	0.45
Recent antibiotic exposure. n (%)	43 (68.2%)	80 (85.1%)	0.01
Mean Charlson Comorbidity index	2.06	0.84	0.001
Recent GI endoscopy procedure, n (%)	5 (8%)	6 (6.3%)	0.75
Acid suppression use, n (%)	17 (27%)	18 (19.2%)	0.25
Severe disease, n (%)	21 (33.3%)	11 (11.7%)	0.001
Metronidazole as Initial treatment *	56/61 (91.8%)	77/89 (86.5%)	0.28
Treatment failure *	16/61 (26.2%)	14/89 (15.7%)	0.15
Recurrence	19 (30.1%)	25 (26.6%)	0.71

* Excluding 7 patients in whom no initial treatment was documented

Table 2

Multiple variable regression model assessing factors associated with the need for hospitalization in community-acquired *Clostridium difficile* infection

	Odds Ratio	95% CI	p-Value
Age*	1.21	1.02-1.43	0.02
Sex			
Female	1.65	0.67-4.12	0.28
Male (reference)			
Charlson Comorbidity index**	1.19	1.01-1.45	0.04
Prior antibiotic exposure			
Yes	0.36	0.15-0.86	0.02
No (reference)			
Severe CDI			
Yes	2.81	1.15-7.13	0.02
No (reference)			

*Unit Odds ratio for every 10-year increase in age

**Unit Odds ratio for every one-unit increase in Charlson Comorbidity index

Table 3

Comparison of clinical features and outcomes in patients with severe disease in community-acquired *Clostridium difficile* infection compared to mild-moderate disease

	Mild-moderate (n=125)	Severe (n=32)	p-value
Age (years), median (range)	46 (1-97)	69.5 (2-102)	0.001
Female, n (%)	94 (78.9%)	25 (78%)	0.72
Antibiotic exposure, n (%)	101 (80.8%)	22 (69%)	0.15
Mean Charlson Comorbidity index	1.22	1.75	0.25
Recent GI endoscopy procedure, n (%)	9 (7.2%)	2 (6%)	0.85
Acid suppression use, n (%)	29 (23.2)	6 (18.8)	0.29
Metronidazole as initial treatment*, n (%)	103/119 (79.3%)	30/31 (96.7%)	0.17
Treatment failure*, n (%)	20/119 (16.8%)	10/31 (32.3%)	0.07
Recurrence, n (%)	32 (25.6%)	12 (38%)	0.19

*Excluding 7 patients in whom no treatment was documented