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Prospective Study

Burden of *Clostridium difficile* infection between 2010 and 2013: Trends and outcomes from an academic center in Eastern Europe

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Abstract

AIM: To analyze the incidence and possible risk factors in hospitalized patients treated with *Clostridium difficile* infection (CDI).

METHODS: A total of 11751 patients were admitted to our clinic between 1 January 2010 and 1 May 2013. Two hundred and forty-seven inpatients were prospectively diagnosed with CDI. For the risk analysis a 1:3 matching was used. Data of 732 patients matched for age, sex, and inpatient care period and unit were compared to those of the CDI population. Inpatient records were collected from an electronic

(54/247 cases). Risk factors for CDI were antibiotic therapy [including third-generation cephalosporins or fluoroquinolones, odds ratio (OR) = 4.559; $P < 0.001$], use of proton pump inhibitors (OR = 2.082, $P < 0.001$), previous hospitalization within 12 mo (OR = 3.167, $P < 0.001$), previous CDI (OR = 15.32; $P < 0.001$), while presence of diabetes mellitus was associated with a decreased risk for CDI (OR = 0.484; $P < 0.001$). Treatment of recurrent cases was significantly different from primary infections with more frequent use of vancomycin alone or in combination ($P < 0.001$), and antibiotic therapy duration was longer ($P < 0.02$). Severity, mortality and outcome of primary infections and relapsing cases did not significantly differ.

CONCLUSION: CDI was accounted for significant burden with longer hospitalization and adverse outcomes. Antibiotic, PPI therapy and previous hospitalization or CDI were risk factors for CDI.

Key words: *Clostridium difficile* infection; Hospitalization; Antibiotics; Proton pump inhibitors

Core tip: *Clostridium difficile* infection (CDI) is one of the most common healthcare-associated infections. It has a high economic burden and its incidence is rapidly increasing in long-term care facilities and acute care hospitals. In the present study, we reported an epidemic of CDI with one of the highest incidences to date. Previous antibiotic treatment, proton pump inhibitor use, previous hospitalization, higher Charlson Comorbidity Index, and previous CDI were identified as predictive factors. CDI was associated with a high healthcare burden, long hospital stay and high mortality.

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burden[4-6].

Previously increasing incidence was only reported in long-term care facilities. In contrast, recent studies report both community onset CDI[7] and acute hospital care onset[8]. Annual incidence of *Clostridium difficile* associated diarrhea and colitis (CDAD and CDAC, respectively) sharply increased from 35 to 156/100000 in past twenty years in Quebec[9]. The increase was more significant in elderly patients, 65 years and above, (number of CDI reports furthermore elevated *via* mandatory surveillance healthcare systems)[10].

Not only did the incidence, but also the number of complicated cases and mortality rates increased[11]. Of note, asymptomatic carriers and colonization of colon microbial flora is observed in about 3% of the population, although in a much higher proportion of patients after long hospital stays and surgery[12]. The spectrum of clinical manifestations associated to *Clostridium difficile* can diverge from asymptomatic carriers to life-threatening infection. CDI symptoms can vary between diarrhea and colitis or enteritisto even life-threatening complicated forms, pseudomembranosus, fulminant colitis or toxic megacolon. Some studies reported decreasing incidence of severe CDI. Feuerstadt *et al*[12] reported improved prognosis and decreased mortality (30-d mortality decreased significantly in both the overall (17.1% *vs* 13.1%, $P < 0.01$) and in the severe CDI (31.3% *vs* 23.3%, $P < 0.05$) cohorts between CDI 2006-2008 and 2009-2011.

Recently reported epidemic and wide-spreading of *Clostiridum difficile* infections are associated with health care associated factors and resistant strains (*e.g.*, NAP1/B027)[13]. Suggested risk factors for developing CDI include prior antibiotic use, acid suppressive agents[14,15], previous CDI[16], comorbidities, malignancies, gastrointestinal disorders[17] and inflammatory bowel diseases[18].

Since there are only limited retrospective data are available from Eastern Europe, our aim was to analyze prospectively the incidence, possible risk factors, treatment strategy and outcome of CDI infections in hospitalized patients, treated at the 1st Department of Medicine, Semmelweis University, Budapest, Hungary.

serology test, including 168 positive and 433 negative result and including recidive cases. Testing density was 5.11/10000 patient-days.

A total of 247 inpatients had a con¿rmed diagnosis of CDI based on the clinical symptoms, laboratory results and cytotoxin stool testing and/or stool culture. Patient data were collected from the hospital electronic database.

Methods

CDI was de¿ned as an acute diarrheal disease (more than three liquid stools per day) with a positive cytotoxin stool assay or a positive cytotoxin stool assay associated with the diagnosis of pseudomembranous colitis by imaging or endoscopic methods, surgery, or autopsy[19]. Repeated exotoxin positivity in 3 mo were defined as recurrence. In our department we apply standardized medical protocols and surveillance guidelines for healthcare associated infections (HAI) including CDI, and thus evaluation of symptomatic patients and treatment strategy is harmonized.

For de¿ning the possible risk factors a 1:3 matching was used. Data of 732 inpatients matched for age, gender, inpatient care period and unit were compared to the CDI population. Inpatient records were collected and comprehensively reviewed, including inpatient ward, co-morbidities (according to Charlson Comorbitiy Index and age-adjusted Charlson Comorbidity Index[20]), medication use (including previous or current antibiotic treatment, proton pump inhibitors and any medication for the treatment of co-morbidities and the current CDI episode), laboratory parameters [white blood cell count (WBC), creatinine, C-reactive protein (CRP), serum albumin level].

Severe CDI was de¿ned as WBC 15 G/L or above and serum albumin level 30 g/L or below based on previous guidelines[21].

Community acquired CDI defined as symptoms developed before hospital admission or less than 48 h after[22].

Three different outcomes were uses, such as recovered, recurrence after healing (within 12 wk), and death. Recurrence was de¿ned as a clinical relapse

analysis by using logistic regression analysis. Variables with a P vaule < 0.1 were included in the multivariate testing. Kaplan-Meier curve was plotted to analyse mortality outcomes with LogRank test. A P value of < 0.05 was considered signi¿cant.

RESULTS

Incidence of CDI and severe CDI

The crude incidence of CDI infection was 21.0 per 1000 all-cause hospital admissions (2.1% of all-cause hospitalizations), 4.45% of total inpatient days were related to CDI (4326/96284 d, equaling 25.6 cases per 10000 patient-days) during the observed period. The majority of the patients were 60 years or older (< 40 years old: 4.7%, 40-60 years old: 11.9%, > 60 years old: 83.4%). Community acquired infection rate was 45.3%. Symptoms were detected at hospitalization in 82 patients (33.2%) and within 3 d from admission in further 30 patients (12.1%). Mean time to presence of CDI symptoms was 2.75 ± 5.3 d from hospital admission.

Total 601 stool sample tested for *Clostridium difficile* infection in Microbiology Department of Semmelweis University, microbiological serology test, including 168 positive and 433 negative result and including relapses. Testing density was 5.11/10000 patient-days.

The incidence of CDI was different according to the unit type, with highest incidence rates in hematology, gastroenterology and nephrology units (32.9, 25 and 24.6/1000 admissions) and lowest rates in 1.4% (33/2312) in endocrinology and general internal medicine (14.2 and 16.9/1000 admissions) units. Incidence did not differ between genders.

The incidence of severe CDI was 12.6% (2.63/1000 of all cause hospitalizations). In severe CDI patients were older (severe: 84.2% *vs* all: 69.6% of patients were > 65 years, P < 0.001) and duration of hospitalization was longer (18.4 ± 11.7 inpatient days *vs* 17.3 ± 10.3 inpatient days, P < 0.001).

Risk factors for CDI

Serum creatinine level, WBC and CRP were higher

	CDI cases (n = 247)	Controls (n = 732)	P value
Age (yr)	72.4 (14.2)	70.6 (13.8)	NS
Male/female	90/157	276/455	NS
Charlson Index	5.6 (3.1)	4.8 (3.0)	< 0.001
Age-adjusted Charlson Comorbidity Index	6.8 (2.7)	5.9 (2.7)	< 0.001
CRP (mg/L)	108.3 (101.3)	49.8 (74.0)	< 0.001
Procalcitonin (mg/L)	1.8 (8.1)	1.2 (12.4)	NS
WBC count (G/L)	14.3 (20.9)	9.9 (8.4)	< 0.001
Albumin (g/L)	29.5 (9.9)	36.2 (11.2)	< 0.001
Creatinine (μmol/ l)	158.3 (158.2)	124.1 (117.7)	< 0.001
Na (mmol/L)	137.7 (14.7)	136.1 (25.1)	NS
K (mmol/L)	4.1 (4.4)	4.4 (4.8)	NS

Data are expressed as mean ± SD. CDI: Clostridium difÀcile infection; CRP: C reactive protein; NS: Not signiÀcant; WBC: White blood cell count.

	Univariate analysis	Multivariate analysis
Gender	P = 0.77	P = 0.47
Previous *Clostridium* difÀcile infection	P < 0.001, OR = 15.3 95%CI: 2.03-48.7	P = 0.08
Previous hospitalization[1]	P < 0.001, OR = 3.17 95%CI: 2.19-4.57	P < 0.001, OR = 2.39, 95%CI: 1.61-3.51
Healthcare facility or nursery home	P = 0.06	P = 0.81
Treatment with "risk" antibiotics	P < 0.001 , OR = 4.56 95%CI: 3.36-6.19	P < 0.001 OR = 4.09, 95%CI: 2.98-5.61
Proton pump inhibitor therapy	P < 0.001, OR = 2.08 95%CI: 1.52-2.85	P = 0.006 OR = 1.62, 95%CI: 1.15-2.29
Charlson Comorbidity Index	P = 0.001	P = 0.004 OR = 1.08, 95%CI: 1.03-1.14

[1]Within 1 year from index hospitalization. Previous "risk" antibiotic therapy: clindamycin, penicillins, third-generation cephalosporins, or Áuoroquinolones. Previous treatment strategy was registered within 1 year from diagnosis of CDI. Proton pump inhibitor therapy was deÀned as at least the suggested daily dose (20 mg omeprazole, 30 mg lansoprazole, or

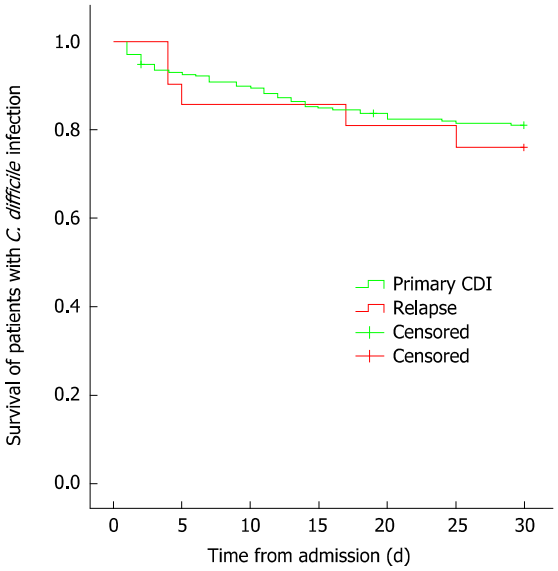

Figure 1 Early mortality of patients with ***Clostridium difficile*** infection. Primary infection vs relapse, within 30 d from admission. P log rank = 0.64. C. Dif¿cile: Clostridium dif¿cile; CDI: Clostridium dif¿cile infection.

Treatment strategy was different in community *vs* hospital-acquired cases with a tendency towards higher metronidazole (P = 0.07) and lower vancomycin (P = 0.004) and/or combination therapy (P = 0.04) rates in the community acquired cases. A similar proportion of the patients required a change of the ¿rst therapy.

The treatment strategy was not significantly different according to the unit type, age or gender (data not shown).

Treatment of recurrent cases was significantly different from primary infections (86.7% vancomycin based including 53.3% combination vancomycin-metronidazole *vs* 29.2% vancomycin-based therapy in primary CDI, P < 0.001). Length of treatment recurrent infections was 16.6 days, longer compared to the primary cases (P = 0.03 *vs* primary CDI).

Outcome of CDI infection

Duration of hospital stay was longer (17.6 ± 10.8 d *vs* 12.4 ± 7.7 d, P < 0.01) in patients with CDI infection

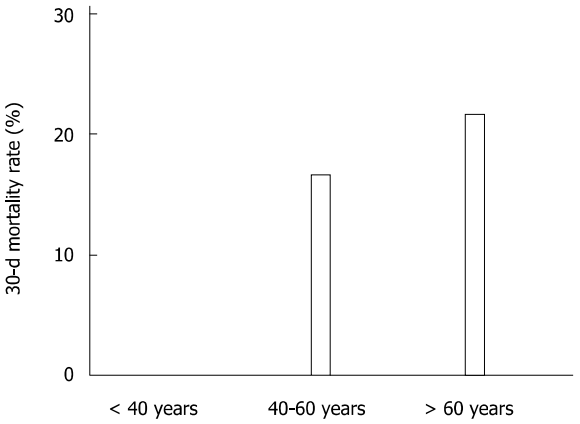

Figure 2 Early mortality in hospitalized patients with Clostridium dif¿cile infection according to the age at admission (within 30-d from admission). P = 0.05 vs different age groups.

DISCUSSION

This is the first prospective systematic evaluation of the incidence, risk factors, treatment and outcomes of CDI in a tertiary academic center in Eastern Europe in inpatients. CDI was associated with a high health care burden and it was responsible for 4.5% of inpatients stays, leading to long hospital stay and high mortality (21.9%). The incidence of severe CDI was 12.6% while recurrence of CDI infection was 11.3% within 12 wk after discharge. Primary CDI infection was initially treated by metronidazole-based regimen, while severe or recurrent cases were significantly more often treated initially with vancomycin, alone or in combination.

Previous studies reported increasing incidence rates from Western Europe and North America. The mean prevalence of CDI increased from 261 to 546 discharged cases per 100000 patients in a nationwide study from the United States between 1993 and 2003[23] (Estimations were based on the discharge data from the Nationwide Inpatient Sample. Similar results were published from another multicenter study between 2000 and 2006. The incidence of hospital-onset CDI increased from 7 to 8.5 cases/10000 unnoticed.

In a multinational European study, the mean incidence of CDI was 4.1 per 10000 patient-days, with 63% of the patients aged 65 years or more as extrapolated from the results obtained in November 2008, from single hospitals[25]. Of note, a significant geographic variation was reported with the highest rate in Finland (19.1 per 10000 patient-days) and the lowest in Turkey and Bulgaria (0 and 0.6 per 10000 patient-days). Interestingly, very low incidences were reported from Eastern European countries including Bulgaria, Croatia, Czech Republic, Romania, Slovakia and Hungary (2 per 10000 patient-days). In contrast, Poland reported one of the highest incidences (12.5 per 10000 patient-days). The incidence in the present study equals 25.6 cases per 10000 patient-days, which is one of the highest reported in Europe, 5 to 10-fold higher compared to the Eastern European data in the multicenter study from 2008.

Few other data are available from Eastern Europe. Surprisingly low, 0.6 per 10000 patient-days incidence rate was reported from a university center from Croatia by Novak *et al*[26] in 2010. Similarly low incidence was reported in a Czech tertiary referral center by Balihar *et al*[27] in 2014, with an incidence of 0.6 per 10000 and 15.8% severe cases, in a retrospective observational study[27]. Finally, the incidence rate in the present study was almost 5-times higher than in the recently published data from Austria (5.23 per 10000 patient-days)[28]. The rate of severe CDI was similar in the present study (12.6%) to that reported from Austria (16.5%). Patients with severe CDI were older and CDI was associated with longer hospital stay. Interestingly, even higher severe CDI rates were reported from the US (20.1%) between 2006 and 2011[12] and from Canada (rising from 7.1% in 1991-1993 to 18.2% in 2003)[9].

Previous antibiotic treatment (clindamycin, amocillin/clavulanic acid, cephalosporins, ciproÀoxacin and Àuoroquinolones), acid suppressive agents, previous hospitalizations, long-term care home residence and comorbidities were previously reported as risk factors for CDI[14-16,29-31]. In concordance, in the present study previous antibiotic treatment with the above

Previous studies suggested a benefit from vancomycin-based treatment strategy, especially in patients with severe CDI preventing adverse outcomes and the development of complicated CDI[9]. In a recent paper from the US, authors reported a shift in the treatment patterns, with shorter duration of oral metronidazole ($P < 0.001$), longer duration of intravenous metronidazole ($P = 0.04$), more frequent use of vancomycin ($P < 0.001$) and more frequent switching from metronidazole to vancomycin ($P < 0.001$) between 2006 and 2011[12]. In the present study, patients received a tailored therapy with increased and earlier use of vancomycin in severe and recurrent cases. Largely similarly treatment data were presented from the Czech Republic[27]. Interestingly, in the present study, treatment strategy was different in community *vs* hospital-acquired cases, with higher metronidazole and lower vancomycin/combination rates in community acquired cases.

Readmission rate (11.3%) in the present study was lower compared to that reported from North America (16%-18%)[12,33] and the Czech Republic (16.4%). However, even lower readmission rates were reported in a multicenter study from Canada (7%)[34]. The average total length of hospital stay in the present study was in the range of previous findings with a mean incremental length of stay of 5.0-13.6 and 2.7-21.3 d for CDI requiring admission and hospital acquired CDI episodes[35]. Of note, much longer mean hospital stay was reported recently from the Czech Republic (median 35 d)[27].

Despite the relatively aggressive treatment strategy, the 30-d mortality rate in the present study was as high as 21.9%. The higher Charlson Comorbidity Index and overall high proportion of elderly patients may at least partly explain this finding. Similar mortality rates were reported recently from the Czech Republic (overall: 19.7%, hospital-acquired: 22.4% and in severe-CDI: 62%) in a cohort with similar age distribution and comorbidity pattern. A mortality rate of 15.2% was reported in a multicenter study from Canada[35]. In another Canadian study death rate in complicated and non-complicated CDI was between the use of vancomycin but not metronidazole was associated with a decreased risk for mortality.

Authors are aware of potential limitations of this study including the possible underestimation of the incidence due to the strict inclusion criteria. Cases were identi¿ed by suggestive symptoms and cytotoxin test positivity, therefore milder cases might have remained unidentified. Demographic data was only partly registered, *e.g.*, nursery home care was not always documented. Conventional treatment methods were used in our university hospital for CDI, including vancomycin and/or metronidazole therapy and patient isolation. The use of new antibiotics, *e.g.*, ¿daxomicin, tigecyclin or fecal microbiota transplantation was exceptional with only one patient evaluated for fecal microbiota transplantation. In the present study, definition of severe CDI was based on Society for Healthcare Epidemiology of America (SHEA) guidelines, but this severity based evaluation was not validated previously. In contrast, the strengths of the present study include the prospective, complete capture. Cases were identi¿ed through the full electronic online in- and outpatient medical records, which is linked to the microbiology and laboratory data, making the search, data capture and analysis extremely reliable. The system contains all out- and inpatient records related to the patient including laboratory data, imaging, hospitalization and/or surgery related hospitalization records from all departments of the Semmelweis University since 2005. In addition, we apply standardized medical protocols and surveillance guidelines in our Department for HAI including CDI, and thus evaluation of symptomatic patients and treatment strategy is harmonized in the different units of the department.

In conclusion, the incidence of CDI was high in this prospective study, and was associated with longer hospital stay and adverse outcomes. Early readmission rates were comparable to ¿ndings of previous studies. A relatively high proportion of patients received aggressive antibiotic therapy and this was tailored to the severity of the cases. Antibiotic therapy, proton pump inhibitor treatment, previous hospitalization and

associated with adverse outcomes, longer hospital stay and high mortality rate. Antibiotic therapy, proton pump inhibitor treatment, previous hospitalization and CDI were risk factors for CDI.

Applications

Understanding the possible risk factors, disease course and outcomes of CDI and treatment strategy in these patient cohort may lead to better optimized treatment strategy and reduced healthcare associated complications.

Terminology

Diagnosis of CDI based on clinical symptoms of diarrhea with positive cytotoxin stool assay or with diagnosis of pseudomembranosus colitis. Comorbidities were categorized according to Charlson Comorbidity and age adjusted Comorbidity Index. Severe infections were defined according to current infection specialists' guidelines (severe leukocytosis and hypoalbuminaemia). Recurrence was de¿ned as relapse of symptoms and positive stool test within 12 wk from discharge.

Peer-review

This is an epidemiological study regarding Clostridium difficile infection in Eastern Europe where its incidence is unclear. The authors present prospective data regarding incidence, risk factors, treatment and outcomes of Clostridium difficile infection. The paper covers an interesting topic and includes a considerable number of patients. They found that antibiotics and proton pump inhibitors were associated with CDI, which confirms the results of previous studies. The epidemiology of CDI is important because CDI remains a major nosocomial infection in the Western world and the epidemiology of CDI appears to be shifting more from healthcare- to community-acquired disease.

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