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THE EPIDEMIOLOGICAL AND CLINICAL ANALYSIS OF *CLOSTRIDIUM DIFFICILE* INFECTIONS IN PATIENTS HOSPITALIZED DUE TO THE INFECTIONS AT THE DEPARTMENT OF INFECTIOUS DISEASES IN BYTOM

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ABSTRACT

Clostridium difficile infections are becoming a more serious problem as hospital-acquired infections and the consequence of common antibiotic therapy, also on an out-patient basis.

AIM OF THE STUDY. The aim of the study was the epidemiological and clinical analysis of patients with *Clostridium difficile*-associated disease (CDAD) at the Clinical Department of Infectious Diseases and Hepatology, Bytom in 2014.

MATERIAL AND METHODS. A retrospective analysis of the medical documentation of patients with the diagnosis of CDAD was performed. The study group was comprised of 24 patients. The following factors were analysed: gender, age, recent hospitalization, use of proton-pump inhibitors, H2-receptor inhibitors, use of antibiotics, co-morbidities, and the clinical course with consideration given to additional laboratory tests (CRP, creatinine, WBC count).

RESULTS. All patients with diagnosed CDAD had been previously hospitalized and 75% of subjects were treated with antibiotics in the period preceding the onset of the disease. Recurrence of the disease was observed in 29% of cases, on average, 12.5 days after hospital discharge. In 16.7% of patients, CDAD resulted in death. Higher CRP concentrations on admission were observed in patients who died compared to the survivors (91.1mg/l vs. 33.6 mg/l, p= 0.015). Additionally, higher concentrations of CRP and leukocytosis were observed in patients with an unfavourable outcome of the disease. Respiratory insufficiency and hypotension were connected with a higher risk of death.

CONCLUSION. Hospitalization, antibiotic therapy, advanced age and co-morbidities may contribute to the occurrence of CDAD. In our study, initially high concentrations of CRP, respiratory insufficiency and hypotension were the predictive factors of a fatal outcome of the disease. The dynamics of changes in the leukocyte value and CRP concentration were of lesser importance.

Key words: *Clostridium difficile, risk factors, hospital-acquired infection*

INTRODUCTION

Clostridium difficile (C. difficile) is a species of gram-positive, anaerobic endospore-forming bacteria, resistant to environmental factors. Spores are not susceptible to high or low temperatures, drying or a number of chemical disinfecting agents. The *C. difficile* bacterium was first described in 1935, its pathogenicity in animals was confirmed in 1969 and since the 1970s a relationship has been observed between the presence of this bacterium and cases of antibiotic-associated colitis in humans (1). It is commonly present in the gastrointestinal tract of humans and animals as well as in the external environment i.e. in the soil and water. The infection is acquired either through the food-borne route as a result of food consumption containing *C. difficile*

or through the faecal–oral route. In hospital settings the reservoir of this bacterium are patients with *C. difficile*-associated disease (CDAD), asymptomatic carriers, healthcare personnel, medical equipment contaminated with *C. difficile* spores and patient surroundings (2,3).

There are both toxin-producing strains as well as strains unable to produce toxins, which are rarely responsible for the occurrence of antibiotic-associated diarrhoea. The pathogenicity of *C. difficile* is associated with the activity of toxins A and B as well as the binary toxin. The spectrum of clinical courses of the infection includes asymptomatic carriage, mild self-resolving diarrhoea and also severe colitis with obstruction. The most common symptom is diarrhoea with cramping abdominal pain, fever and leukocytosis. Pseudomembranous colitis with the presence of the so-called pseudomembranes is highly specific for the diagnosis of CDAD and occurs in clinically more severe courses of the disease. The most severe forms of the disease with the symptoms of acute abdomen, bowel obstruction or megacolon require surgical intervention. *Clostridium difficile*-associated diarrhoea results in the highest mortality rate among diarrhoeas of infectious aetiology in young persons without additional co-morbidities (4). Extraintestinal *C. difficile* infections are possible though not common and are related to the abdominal cavity or contaminated wounds (5).

The following are the documented risk factors for CDAD: the use of antibiotics, especially of broad-spectrum, hospitalization or stay in nursing homes, age > 65 years old, the use of proton pump inhibitors (PPIs) and H_2-receptor antagonists, chemotherapy, immunosuppression, surgical procedures, feeding tubes and co-morbidities (6). The diagnosis of CDAD is associated with a high rate of recurrence (i.e. 20%) (7).

According to the reports from the USA, *C. difficile* infection is currently the most frequent hospital-acquired infection and has surpassed the infection with methicillin-resistant *Staphylococcus aureus* (8). The problem is also growing in Europe and starts to occur in Asia and Australia (9, 10). Based on the data from the EUCLID Project, an increase in the incidence of infections was observed in Europe between 2012 and 2013. The increase was reported from 6.6 to 7.3 cases per 10 000 in-patient bed-days based on hospital reports and a decrease from 19.0 to 17.2 based on the tests performed by referral laboratories. The data concerning Poland indicated a decrease in the incidence of *C. difficile* infection from 8.6 to 8.2 based on reports and an increase from 29.4 to 48.3 based on the tests in referral units. Both data concerning Europe and Poland demonstrate an underestimation of CDAD cases (11). According to the National Institute of Public Health – National Institute of Hygiene (Poland), the incidence of *C. difficile* infection in 2013 and 2014 was 12.3 and 16.7, respectively, which corresponded to 4738 and 6425 cases (12, 13).

The increase in the incidence and mortality is partially associated with the occurrence of an epidemic strain of *C. difficile* NAP1 (North American Pulsed Field Type). It is characterised by an increased secretion of toxins A and B, the production of the binary toxin, enhanced ability of spore production and a clinically more severe course of infection. This strain was first isolated in Poland in 2005 (14).

AIM OF THE STUDY

The aim of the study was the epidemiological and clinical analysis of patients hospitalized at the Clinical Department of Infectious Diseases and Hepatology, Medical University of Silesia with the diagnosis of CDAD. The assessment of risk factors, severity of the course of the disease and effectiveness of therapy was made.

MATERIAL AND METHODS

A retrospective analysis of medial documentation was performed in 24 patients hospitalized at the Clinical Department of Infectious Diseases and Hepatology, Medical University of Silesia in whom CDAD was diagnosed between 1st January 2014 to 31st December 2014 (Table I).

Table I. Patient characteristics, co-morbidities and symptoms occurring in the course of CDAD

Age: median (quartile deviation)	74 years (7)
Male gender (%)	17 (70.8%)
Use of antibiotics prior to the development of symptoms	18 (75.0%)
Use of IPPs	11 (45.8%)
Co-morbidities: - ischaemic heart disease - arterial hypertension - diabetes mellitus - chronic heart failure - chronic renal failure - hypothyroidism - anaemia - gastric and/or duodenal ulcer disease - pneumonia	 15 (62.5%) 11 (45.8%) 10 (41.7%) 8 (33.3%) 6 (25%) 3 (12.5%) 3 (12.5%) 2 (8.3%) 1 (4.2%)
Patients on immunosuppression	3 (12.5%)
Hypotension	4 (16.7%)
Fever > 38.5˚ C	4 (16.7%)
Renal failure	2 (8.3%)
Respiratory insufficiency	2 (8.3%)
Intestinal obstruction	0
Encephalopathy	0
Necessity of surgical treatment	0
Death	4 (16.7%)

Tests for *C. difficile* infection were conducted in patients admitted with symptoms of acute diarrhoea or the occurrence of diarrhoea during hospital stay. A two-stage procedure of stool specimen testing was used - the EIA test for the detection of GLDH antigen (glutamate dehydrogenase) and in the case of a positive result the latex agglutination test for detection of toxins A/B. The diagnosis of CDAD was made if the presence of toxins A/B in stool was confirmed and other causes of acute diarrhoea were excluded (15). The analysis included the following: age, gender, previously taken antibiotics, PPIs and H2-receptor antagonists, co-morbidities, history of hospital stay and the course of the disease with consideration given to the results of selected additional tests (i.e. CRP, creatinine, WBC count).

The test results were described using the measures of location. The distributions of quantitative variables were analysed using the Shapiro-Wilk test. The Mann-Whitney U test was applied due to the fact that the majority of distributions were not close to the normal distribution. The level of significance was set at $p = 0.05$. Statistical significance of the relationship between two variables of dichotomous nature was analysed using the test and the strength of relationship was assessed using the Yule's association coefficient (). Statistical analysis was performed using Statistica v.10 (StatSoft Inc., Tulsa, OK, USA).

RESULTS

All 24 patients observed at the department had been hospitalized prior to the occurrence of symptoms of the disease and 22 fulfilled the diagnostic criteria for hospital-associated diarrhoea. Eighteen patients received antibiotics during and/or before hospital stay (most commonly ciprofloxacin, and next in the following order: amoxicillin with clavulanic acid, cefuroxime, cefotaxime and amikacin). Table II presents the length of hospitalization, duration of antibiotic therapy and the time to potential recurrence (in 7 patients).

Ten patients (41.7%) were treated with metronidazole (3x500 mg p.o. for 10-14 days), 8 patients (33.3%) with vancomycin (4x125-500 mg p.o. for 10-14 days). Five patients (20.8%) were initially administered oral metronidazole, however, due to no response after 5 days these patients were switched to oral vancomycin (10-14 days). One patient (4.1%) was treated with both metronidazole (3x500 mg i.v.) and vancomycin (4x500 mg p.o.) for 14 days.

Table II. The analysis of the duration of antibiotic therapy, length of hospitalization prior to the onset of the symptoms of the disease and time to recurrence (days)

Parameter	median (quartile deviation) days
Length of hospitalization prior to the onset of symptoms (N = 14)	10 (4.75)
Duration of antibiotic therapy prior to the onset of symptoms (N = 9)	12 (3.5)
Time to disease recurrence (N = 7)	12.5 (11)

In 4 patients (16.7%) the course of the disease was severe and resulted in death. In 3 cases the direct cause of death was an exacerbation of chronic heart failure in the course of CDAD and in 1 case pneumonia with respiratory insufficiency as a complication of CDAD.

No differences were observed in the severity of the disease course depending on the gender or age. Patient characteristics with the list of co-morbidities and symptoms occurring during hospital stay are presented in Table I.

The Mann-Whitney U test was used to determine differences between test results and the risk of death in the patient. However, no statistically significant differences were observed in the concentration of serum creatinine or WBC count measured on admission between patients who died in the course of the disease and patients in whom recovery was observed. Higher concentrations of CRP on admission were confirmed in patients who died in the course of hospitalization as compared to patients who were successfully treated. Higher leukocytosis and higher concentration of CRP were observed at the end of hospital stay in patients whose treatment was unsuccessful (Table III).

Table III. Median of the laboratory test results in CDAD patients

Test	Outcome of hospitalization		P
	recovery	death	
Creatinine concentration on admission (mmol/L)	92.0	87.9	1.000
WBC count on admission (G/L)	10.5	15.4	0.261
CRP concentration on admission (mg/L)	33.6	91.1	0.019*
WBC count prior to the end of hospitalization (G/L)	6.04	15.3	0.013*
CRP concentration prior to the end of hospitalization (mg/L)	16.3	91.1	0.018*

* $p < 0.05$

None of the hospitalized patients presented with encephalopathy or intestinal obstruction. No surgical intervention was required either. The following were observed: hypotension, respiratory insufficiency, renal failure, fever >38.5˚C (Table I). Two dichotomous variables were compared (death during hospital stay and the presence of one of the above-mentioned clinical conditions). Moderate correlation was observed in the case of respiratory insufficiency (statistically significant,

with) and hypotension (statistically significant, with). However, no statistically significant relationship was noted between renal failure or fever and death during hospital stay. The type of treatment (metronidazole and/or vancomycin) did not have a statistically significant influence on the occurrence of death either.

DISCUSSION

Males were predominant in the analysed group. However, the gender was not a risk factor for CDAD. Other authors also confirmed that the gender did not constitute a risk factor. However, attention was paid to a higher percentage of female patients in the general population with CDAD (16, 17), which was contrary to the observations in our study.

Age >65 years is considered a risk factor for CDAD (18). Only 6 patients were younger in the analysed group. Some of the researchers do not confirm the correlation between age and CDAD (16). However, age is commonly regarded as a risk factor for recurrence, a severe course of the disease and death (19, 20). Among the analysed patients recurrence was observed in 7 cases (mean age 77.1 years) and 4 patients died (mean age 73.7 years).

The following are the antibiotics which particularly predispose to the occurrence of CDAD: fluoroquinolones, amoxicillin with clavulanic acid and cephalosporins, especially the third generation cephalosporins (16). In our study group, 18 patients (75%) had been taking antibiotics prior to the onset of CDAD. Patients received ciprofloxacin, amoxicillin with clavulanic acid, cefuroxime and in 1 case amikacin with cefuroxime. The symptoms of CDAD were observed, on average, after 12 days of antibiotic therapy, which in some cases started prior to hospital admission.

All analysed patients had been hospitalized prior to the onset of CDAD. The mean length of hospital stay was 10 days. Recent or ongoing hospitalization constitutes an important risk factor for CDAD even if it is not connected with antibiotic treatment (18). It may be the result of more frequent *C. difficile* carriage among hospitalized patients as compared to the general population (21), medical procedures applied (6) or conditions of hospitalization (22). Proper surveillance allows to reduce the incidence of CDAD as a hospital-acquired infection. Currently, an increase in the incidence of CDAD infection is observed, however with no relation to hospital treatment. This group of patients is significantly different from the previously discussed. Patients are usually younger, have a less frequent history of past antibiotic therapy and a more frequent history of PPI use (23).

Numerous reports indicate a relationship between PPI use and the occurrence of CDAD (6). Apart from changes in gastric juice pH, a decreased expression of genes which are crucial for colonocyte integrity may also be the cause of CDAD (24). The use of PPIs may be associated with an increased risk of disease recurrence (25). The reports of other researchers do not confirm these findings (26). In the analysed group, 11 patients (45.8%) had used PPI prior to the occurrence of CDAD symptoms. It was 1.5 times more frequent compared to patients hospitalized due to other reasons. However, no statistically significant differences were observed. Comorbidities are considered to be factors predisposing to the development of CDAD (27).

A clinical course of CDAD varies, ranging from mild diarrhoea to severe colitis resulting in death. Various classifications for determining and predicting the severity of the disease are suggested. The variables used for this purpose include the following laboratory parameters: albumin concentration, leukocytosis, serum lactic acid concentration, serum creatinine concentration as well as clinical features such as hypotension, fever, intestinal obstruction, respiratory insufficiency, renal failure and encephalopathy. Our study analysed the relationship between the selected laboratory and clinical parameters, and the risk of death. No statistically significant differences were observed between the serum creatinine concentration or leukocytosis on admission and the risk of death. However, a tendency to a higher leukocytosis was noted in patients in whom treatment did not result in successful outcome. Leukocytosis prior to death of the patient was significantly different from the values obtained by patients treated successfully. It seems that the assessment of the dynamics of this parameter may be useful in the prognosis. In the study of Butt *et al.* leukocytosis > 12.0 G/L constituted one of the four variables associated with the risk of death (28). In our study the value in the group of patients who died was, on average, 15.4 G/L.

Our observations concerning CRP concentration were similar to those presented by Butt *et al.* In the analysed group higher concentrations of CRP were observed on admission in patients who died. According to Butt *et al*., CRP concentration > 228 mg/l is associated with an increased risk of death, the remaining variables being leukocytosis (discussed above), low albumin concentration and respiratory rate >17/min.

Among the analysed general symptoms accompanying the disease, respiratory insufficiency was associated with the risk of death, next to the decreased values of arterial pressure. The type of antibiotic used in the treatment did not have a statistical influence on the risk of death occurrence.

CONCLUSIONS

Clostridium difficile is a bacterium that commonly exists in the environment. The colonisation by this pathogen is particularly frequent in hospital settings. In recent years there has been an alarming increase in the incidence of CDAD. Risk factors such as hospitalization, antibiotic therapy, age, co-morbidities contribute to the occurrence of the disease.

The present study confirmed the relationship between CDAD and a history of hospital stay, antibiotic therapy and advanced age.

Initially high concentrations of CRP, respiratory insufficiency and hypotension were the predictors of death. The dynamics of changes in the leukocyte value and CRP concentration was also significant, however to a lesser extent.

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