ORIGINAL ARTICLE

UPDATES IN THE ASSESMENT OF RISK FACTORS IN *CLOSTRIDIUM DIFFICILE* INFECTION IN PATIENTS WITH INFECTIOUS DISEASES

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Abstract

Infection with *Clostridium difficile* has become increasingly more frequent in recent years, being currently one of the most common aetiology of diarrheal disease. The aim of our work was to broaden the current knowledge of the *Clostridium difficile* digestive infections in patients admitted to the Infectious Diseases Hospital from Iasi City, Romania. We have studied 166 patients with *Clostridium difficile enterolactis*, hospitalized between 01.01.2014 - 31.03 2015. We have found an increasing trend in the number of cases between December 2014 and March 2015, particularly among immunocompromised patients, 48% of cases occurred in patients with previous surgery area and 57% came from medical services. Investigation of the used groups of antibiotics revealed that the highest risk is the use of fluoroquinolones, followed by cephalosporins. Relapses were found in 28.67% cases, and treatment was performed with Metronidazole (66.26%), Vancomycin (5.42%) and Vancomycin + Metronidazole (28.31%). Analysis of cases is a warning on unjustified and irrational use of antibiotics and the danger of nosocomial infections.

Rezumat

Infecţia cu *Clostridium difficile* a devenit în ultimii ani din ce în ce mai frecventă, ajungând în prezent una din cele mai des întâlnite etiologii a bolii diareice. Obiectivul studiului a fost reprezentat de analiza infecţiilor digestive cu *Clostridium difficile* la pacienţii internaţi în Spitalul Clinic de Boli Infecţioase Iaşi. Au fost studiaţi 166 pacienţi cu enterocolită cu *Cl. difficile*, internaţi în perioada 1.01.2014 - 31.03.2015. S-a constatat o tendinţă de creştere a numărului de cazuri în perioada decembrie 2014 - martie 2015, mai ales printre pacienţii imunodeprimaţi, 48% din cazuri au survenit la pacienţii cu intervenţii chirurgicale în antecedente apropiate, iar 57% proveneau din servicii medicale. Investigarea grupelor de antibiotice utilizate a relevat faptul că cel mai mare risc îl induce utilizarea de fluorochinolone, urmat de cefalosporine. Recăderile au fost constatate la 28,67% din cazuri, iar tratamentul a fost realizat cu: Metronidazol (66,26%), Vancomicină (5,42%) şi Vancomicină + Metronidazol (28,31%). Analiza cazurilor reprezintă un semnal de alarmă referitor la consumul nejustificat şi iraţional de antibiotice precum şi la pericolul apariţiei de infecţii intraspitaliceşti.

Keywords: *Clostridium difficile*, risk factors, infectious diseases

Introduction

In recent years, infections with *Clostridium difficile* (CDI), have become increasingly common, between cases of antibiotics associated diarrhoea (20% - 30%), and is the most frequent known cause of infectious diarrhoea in healthcare centres [1-3]. *Clostridium difficile* causes various symptoms, ranging from asymptomatic to mild or severe diarrhoea that can endanger the patient's life [4]. In the US in 2010 there were registered 346,800 hospitalized cases with *Clostridium difficile* infection, with 30,000 deaths, because CDI is 21% more common than Methycillin resistant *Staphylococcus aureus* (MRSA) [5-7]. In Europe, CDI rate is 4.1/10,000 patients per day, with a mortality of 22% at 90 days. The economic impact of CDI is in Europe approximately $ 3 billion/year (CDI patient care in hospitals) and in US riche 1.3 billion/year. *Clostridium difficile* is a Gram positive, anaerobic, sporulated ubiquitous bacterium, present in: faecal flora (60-70% in neonates, 10-30% in hospitalized patients, 3% in healthy adults), genitourinary tract (18-71%), manure of various animals and birds, in lakes, in pools, sand, dust (Pakistan), hospital units and healthcare centres [8-10]. It takes two forms:

vegetative –inactivated by atmospheric oxygen, spores - resistant to disinfectants and antiseptics. Pathogenic strains of *Clostridium difficile* produce two distinct toxins: toxin A (enterotoxin – toxic action, lethal, responsible for clinical symptoms) and toxin B (cytotoxin – exerts cytopathic effect - laboratory diagnosis). Both toxins play a role in *Clostridium difficile* colitis pathogenesis in humans. The risk factors are: age over 64 years, duration of hospitalization, antimicrobial agents, chemotherapy, gastrointestinal surgery, antacids, mirtazapine and fluoxetine (antidepressants) treatment [11-14]. The aim of this study is derivative from the need to knowledge the aspects of the emergence of this disease in the last period in our region. The conducted research focused on epidemiological, clinical and evolutionary peculiarities of *Clostridium difficile* infection in patients hospitalized and treated in Iasi City Infectious Diseases Hospital between January 2014 and March 2015. The study aims were to assess the clinical and epidemiological features of *Clostridium difficile* infection by establishing the influence of risk factors involved in the occurrence of *Clostridium difficile* infection in the patients enrolled in the study (166 patients), to determine correlations between risk factors and clinical-evolutionary aspects of the patients establishing correlations between prognostic risk factors, comorbidities and disease severity.

Materials and Methods

It has been conducted a retrospective study between January 2014 and March 2015, 166 patients being included, using the following inclusion criteria: presence of diarrheal syndrome, positive test for *Clostridium difficile* toxin, suggestive aspects of pseudo-membranous colitis observed during colonoscopy, response to specific antibiotics for pseudo-membranous colitis and exclusion criteria: diarrheal syndrome of other type of aetiology, the response to symptomatic treatment and/or empirical antibiotics for suspected bacterial aetiology diarrhoea.
All patients with flare activity were tested for diagnosis using immune-chromatography assay for toxins A and B. The results were statistically processed using: student "t" test, χ^2 test, and the relative risk (RR). We have used the RR score for calculating the major risk in diabetic patients. The relative risk (RR), its standard error and 95% confidence interval are calculated according to Bhangu and Altman [3]. The following risk factors of CDI were assessed: incidence, age, sex, co-morbidities, cause, and antibiotics.

Results and Discussion

Comparative analysis of pseudo-membranous colitis distribution, by years of study, revealed the following: in the first 12 months were diagnosed 109 cases, in a relatively equal distribution according to the gender (female 54 cases, male 55 cases); in the first 3 months of 2015 there has been a marked increase in the cases of pseudo-membranous colitis, 57 patients (Figure 1). It should be noted a slightly higher percentage of female cases in the period January-May 2014 (female 32 cases, male 25 cases), the yearly distribution of pseudo-membranous colitis *Clostridium difficile* percentage having no significant gender difference (p = 0.478) [3].

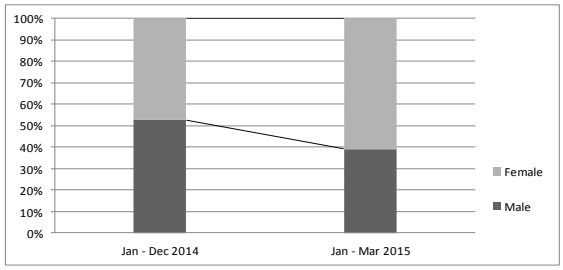

Figure 1.
Yearly distribution of cases with *Clostridium difficile* pseudomembranous colitis by gender

Patients' age ranged between 35 and 60 years (Figure 2), with a predominance of females depicted in Figure 3.

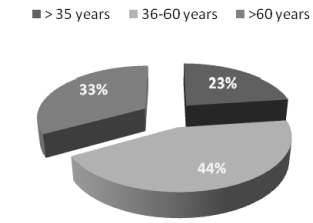

Figure 2.
Distribution of the total number of patients by age

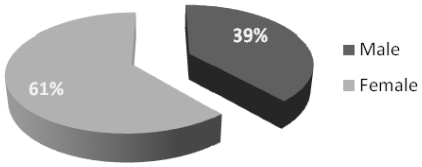

Figure 3.
The distribution of patients according to sex

Depending on patient's previous medical history, the greatest risk was registered for diabetic patients (RR = 2.63) and for digestive symptoms patients (RR = 1.79) (Table I).

Table I
Personal pathological antecedents - comorbidities

Co morbidities	N	%	χ^2	p	RR	IC95%
Digestive	8	12.1	5.85	**0.016**	1.79	0.87÷3.66
Renal	14	15.5	8.42	**0.004**	1.32	0.69÷2.49
Malignancies	10	13.9	7.11	**0.008**	1.52	1.01÷2.99
Diabetes	6	8.6	3.50	**0.026**	2.63	1.12÷6.15

The smallest risk was noted for patients with renal diseases as comorbidities.

In hospital, the major risk factor is represented by exposure to antimicrobial agents, especially to Clindamycin and β-lactamines. We also identified other potential risk factors for CDI: the administration of protons pomp inhibitors, the presence of intestinal inflammatory diseases or irritable bowel syndrome. During the hospitalization, the prevalence in the first 7 days was 1% to 20%, increasing to 50% for at least 4 weeks. We also assessed early symptoms of infection with *Clostridium difficile*, likewise debut in the community - patients having a history of surgery; associate debut in hospital health care; undefined debut - patients hospitalized 4-12 weeks prior to the early symptoms; community debut - without hospitalization in the last 3 months.

There has been a growing trend in the number of cases between December 2014 and March 2015, particularly among immunocompromised patients (cancers, diabetes, liver cirrhosis, chronic renal failure). 48% of cases occurred in patients after recent surgery and 57% came from medical services. Causes of developing CDI are shown in Figure 4.

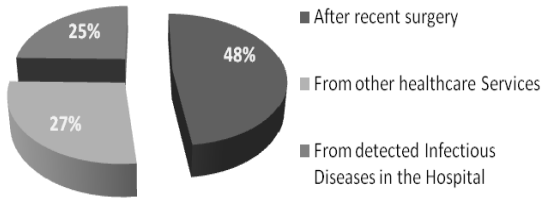

Figure 4.
Causes of developing CDI

In terms of the abdominal discomfort, patients were suffering pains in more than 90% of cases, either diffuse or colicky pain. It is well known that the main risk factor is represented by the exposure to antimicrobial agents, especially Clindamycin and β-lactamines. Continuing the study using groups of antibiotics, it revealed that the highest risk is represented by the use of fluoroquinolones followed by cephalosporins (Figure 5).

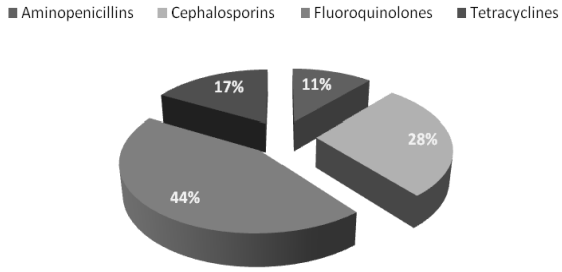

Figure 5.
The study group of antibiotics as a cause of CDI

Unfortunately relapses were recorded in 28.67% of the cases. The treatment was carried out as follows: Metronidazole (66.26%), Vancomycin (5.42%) and Vancomycin + Metronidazole (28.31%). The treatment impact during the study period was successfully for 135 patients and relapsed for 31 patients.

During the antibiotic treatment of CDIs the antibiotic resistance and physiological factors of the bacteria (spore formation, protective effects of the pseudo-membrane) may cause difficulties. The emergence of a new and highly toxic strain of *Clostridium difficile* resistant to fluoroquinolone antibiotics (such as Ciprofloxacin and Levofloxacin), which determine geographically dispersed outbreaks in North America, was reported in 2005. The United States Centers for Disease Control and Prevention in Atlanta warned about the emergence of an epidemic strain with increased virulence, antibiotic resistance, or both. Like prognosis, after a first treatment with Metronidazole or Vancomycin, *Clostridium difficile* recurs in about 20% of the cases, increasing 40% and 60% with subsequent recurrences [15, 16].

Conclusions

Analysis of the cases with *Clostridium difficile* infection is a state on unjustified and irrational use of antibiotics and also a warning represented by nosocomial infections. We found an increasing trend of the number of cases between December 2014 and March 2015 particularly among immuno-compromised patients, 48% of cases occurred in patients after recent surgery and 57% came from medical services. The treatment was carried out with: Metronidazole, Vancomycin and Vancomycin + Metronidazole. The treatment with antibiotics, known as a risk factor in development of *Clostridium difficile* pseudomembranous colitis, has been documented in our study investigating the antibiotics groups, revealing that the highest risk is represented by the use of fluoroquinolones and cephalosporins. Our study is warning once more on the unjustified and irrational use of antibiotics, as well as on the danger represented by nosocomial infections.

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