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RESEARCH ARTICLE

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Factors Favouring the Development of Clostridium Difficile Infection in Critically Ill Patients

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Abstract

Clostridium difficile, an anaerobic, spore-forming, toxin-forming, gram-positive bacillus present in the bacterial flora of the colon is the principal cause of nosocomial diarrhoea in adults.

Aim: Assessment of favouring factors of Clostridium difficile infections as well as the interactions between them, in critically ill hospitalized patients undergoing complex medical and surgical treatments.

Material and Methods: A retrospective case-control study involving eighty patients admitted in the Intensive Care Unit (ICU) of the County Clinical Emergency Hospital Tîrgu-Mureş was conducted between January and October 2014. Patients aged eighteen years and over, who had undergone complex medical and surgical treatment, were divided into two subgroups. Group 1 included patients who developed diarrhoea but were not diagnosed as having a Clostridium difficile infection (CDI). Group 2 included patients who developed diarrhoea due to CDI as indicated by a positive culture and the expression of exotoxin. The assessed parameters were age, length of stay (LOS), antibiotic spectrum, association with proton pump inhibitors (PPI) or H2-receptor antagonists, immunological status, the presence or lack of gastrointestinal tract surgery.

Results: The mean age was 64.6 years with an average LOS of 10 days. Fifty-six percent of patients came to the ICU from internal medicine wards and forty-three percent from surgical wards. 20.5% of them were immunosuppressed. Co-association of ceftriaxone and pantoprazole significantly increased the risk of CDI compared to co-administration of any other antibiotic or pantoprazole (p=0.01). The odds ratio for Pantoprazole together with any antibiotic versus antibiotic therapy alone was significantly higher (p=0.018) with a sevenfold increase in the risk of positive exotoxin increase.

Conclusions: Antibiotic use is associated with “no risk to develop CDI” in the first five days of administration. PPIs associated therapy increased the risk of CDI in first seventy-two hours regardless of the antibiotic type, and contributes to an active expression of CD exotoxin.

Keywords: nosocomial infection, Clostridium difficile, Pantoprazole, antibiotic therapy

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Introduction

Clostridium difficile (CD) is an anaerobic, spore-forming, toxin-forming, gram-positive bacillus that is present in the bacterial flora of the colon. It is the leading cause of nosocomial diarrhoea in adults. It impacts considerably on the length of hospital stay (LOS) and medical costs [1,2]. The incidence and the mortality rate due to Clostridium difficile infection (CDI) have increased in the last two decades. Recent epidemiological reports indicate that infection with methicillin-re-

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sistant Staphylococcus aureus is replaced by CDI as the most common nosocomial infection [3,4]. The virulence of CD is due to the associated production of enterotoxin A and cytotoxin B, which are responsible for a range of clinical conditions including colonic and extracolonic manifestations ranging from asymptomatic carriage to toxic megacolon [3,5]. McDonald et al. [6] showed that a mutant hypervirulent strain, NAP1/BI/027, produces more toxin A and toxin B in addition to the binary toxin then other strains. This finding could explain the increasing severity of CDI. Despite this hypervirulent strain of CD, several subpopulations are disproportionately affected due to presence or absence of one or more risk factors. The most important risk factors include male gender, age >65 years, recent antibiotic exposure, PPI use, and prolonged LOS. The presence of underlying conditions such as inflammatory bowel diseases, immunodeficiency, HIV, neoplastic diseases, gastrointestinal surgery, malnutrition, serum albumin levels < 2, 5 g/dL, diabetes mellitus and cystic fibrosis [7] also contribute to increased risk.

In the last two decades, the irrational and routine use of PPIs in ulcer prophylaxis is associated with an increased incidence of colonization by the commensals from the colon to the upper gastrointestinal tract. The gastric juice is bactericidal at a pH less than< 4.0 but is ineffective at a pH> 6.0. PPIs therapy elevates gastric pH and this is associated with an increased risk of a CD superinfection and diarrhoea [8].

The aim of our study is the assessment of etiopathogenic and favouring factors of CDI as well as the interactions between them, in hospitalized critically ill patients undergoing complex medical and surgical treatment. We hypothesized that PPIs treatment and length of therapy was not associated with CDI and we considered antibiotic therapy as a risk factor in CDI development.

Material and Methods

A retrospective case-control study was conducted on patients admitted in the Intensive Care Unit (ICU) of the County Clinical Emergency Hospital Tîrgu-Mureș, Romania between January and October 2014. Prior approval was obtained from the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu-Mureș, Romania. Eighty patients aged eighteen years and over were admitted to the study. Inclusion criteria were set to be critical patients over the age of eighteen, admitted to the Intensive Care Clinic for a longer period then three days, all receiving single drug or multiple antibiotic therapies, all receiving stress ulcer prophylactic treatment and with no known CDI in their history. We set the three-day marker for length of stay (LOS) because hospital-acquired CDI requires a positive test result no earlier than three days into the admission [9]. All patients underwent complex medical treatment like mechanical ventilation, renal replacement therapy, coronary revascularisation, as well as complex surgical treatment, such as upper gastrointestinal tract surgery and colonic surgery. They were divided into two subgroups: Group 1 consisted of patients who developed diarrhoea without CDI and Group 2 consisted of patients who developed diarrhoea associated with CDI. All patients in the study had episodes of diarrhoea, and 77.5% of them received PPIs (pantoprazole or omeprazole). The remaining 22.5% received either Histamine-2 Receptor Antagonists (H_2RAs) as ranitidine or no acid suppression drug.

Parameters assessed were age, gender, LOS, antibiotic spectrum, proton pump inhibitors or H_2RAs therapy, immunological status, lack or presence of surgery on the gastrointestinal tract.

The presence of CDI was confirmed using a positive Clostridium difficile toxin assay and a positive culture from liquid stool obtained at least seventy-two hours after admission.

Statistical analysis included Chi-square (χ^2) tests and logistic regression models. For normally distributed data mean and standard deviations were reported and for non-normally distributed data the median and interquartile range were given. Normality was tested using the Shapiro-Wilk test. The level of significance was set to 0.05. Logistic regression analysis was used to assess the risk factors for CDI. The data was analyzed using SPSS v.20 (2013 Chicago, USA).

Results

52.5% of patients were male and 47.5% female, with a mean age of 64.6 years (SD ± 15.4). 1.2% of patients developed one or two organ dysfunctions. Approximately 56% of patients came from medical wards, and 44% from surgical wards. 20.5% of all patients were undergoing immunosuppressive treatment or were immune compromised. The average LOS in the ICU was ten days and the risk to develop CDI was higher

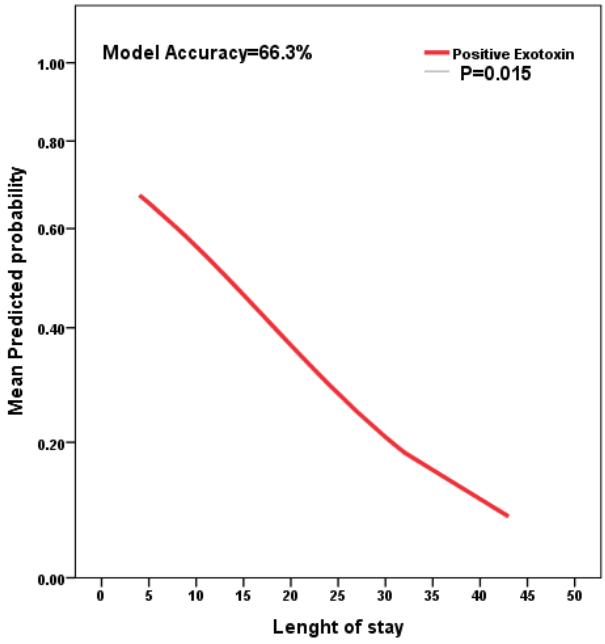

Fig. 1. Logistic regression model for length of stay in patients with Clostridium difficile infection

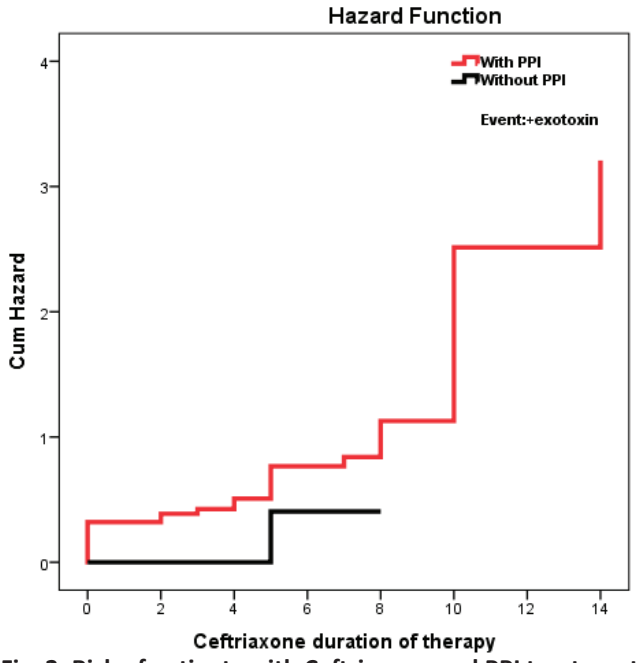

Fig. 2. Risk of patients with Ceftriaxone and PPI treatment in developing CDI

in the first ten days of hospitalization (p=0.0015) with increased risk of CDI in patients receiving early PPI therapy (p=0.001).

The reported accuracy of the logistic model was 66.3%, with a mean probability of developing an infection of ~ 60% in the first ten days (p=0.015) (Figure 1).

We summarized the antibiotic regimens and mean days of administration. The highest rate of administration was reported for ceftriaxone (37.4%), with a mean administration time of 2.85 days until diarrhoea occurrence (Table 1).

Using the logistic regression model only ceftriaxone treatment accounted as a risk factor for developing CDI (p=0.007) (Figure 2). The danger of combined antibiotic and PPI therapy increased the risk of early Clostridium difficile infection during a hospital stay.

The risk of double therapy increases the risk of infection early in the administration period. Without PPIs

Table 1. Antibiotic summary

	Frequency (patients)	Percent (%)	Mean Days (days)	Std.Dev (days)
Colistin	2	2.0	0.13	±0.91
Vancomycin	3	3.0	0.3	±2
Linezolid	1	1.0	0.1	±0.89
Cefoperazone	3	3.0	0.23	±1.14
Tazocin	1	1.0	0.05	±0.447
Metronidazole	12	12.1	0.91	±2.26
Levofloxacin	2	2.0	0.01	±0.0001
Amikacin	1	1.0	0.05	±0.447
Teicoplanin	4	4.0	0.35	±1.592
Meropenem	15	15.2	1.3	±3.22
Imipenem	5	5.1	0.23	±1.27
Ceftriaxone	37	37.4	2.85	±4.13
Cefuroxime	2	2.0	0.16	±1.04
Ciprofloxacin	11	11.1	0.85	±2.48

co-administration, the risk of infection solely due to ceftriaxone is 0 for approximately five days. Therefore, the risk of infection is attributable to PPI administration (Figure 3).

The odds ratio for ceftriaxone-pantoprazole treatment regarding infection was 3.5 (p=0.01, χ^2 test) when the outcome was positive exotoxin and 4.9 (p=0.002, χ^2 test) when the outcome was positive stool culture (Figure 4).

There was a significant difference when antibiotic type was compared.

The odds ratio for developing an infection in patients who received pantoprazole was 7.35 (p=0.0001, χ^2 test) when the outcome was positive exotoxin and 8.8 (p<0.0001, χ^2 test) when the outcome was positive stool culture.

The odds ratio for developing an infection with PPI administration was 11.3 (p=0.000021, χ^2 test) when the a positive stool culture was obtained, and 11.2 when there was a positive exotoxin expression. (p=0.00002, χ^2 test) (Figure 5).

There was no risk of infection associated with LOS in patients not receiving PPIs but increased with LOS in patients receiving these drugs (Figure 6).

Only the PPIs therapy and LOS were associated with a risk of infection.

Discussion

The aim of this study was the assessment of etiopathogenic and favouring factors of CDI as well as the interactions between them, in hospitalized patients. We started from the premise that PPIs treatment and length of therapy is not associated with CDI. We considered antibiotic therapy as a risk factor in CDI development. The results of the study refute the null hypothesis.

CDI is defined as laboratory confirmation of a positive Clostridium difficile toxin assay and a positive culture from liquid stool obtained at least seventy-two hours after admission, because hospital-acquired CDI requires a positive test result no earlier than three days into the admission [9].

CD is well known to be a primary cause of hospital-acquired colitis in patients receiving antibiotics, immunosuppressives, PPIs or chemotherapy [5]. The increased severity and incidence of CDI are due to the selection of a much more virulent strain of bacteria, NAP1/B1/027, with toxin A and B hyperproduction due to one tcdC gene deletion [10].

The physiopathological mechanisms are related to three evolutionary stages: 1. The alteration of intestinal microbiota following anti-biotherapy. 2. Bowel infection and colonization with a virulent toxin-producing strain of CD. 3. The transformation from spore to vegetative form in the intestine, with the release of toxin A (enterotoxin) and B (cytotoxic) [10,11].

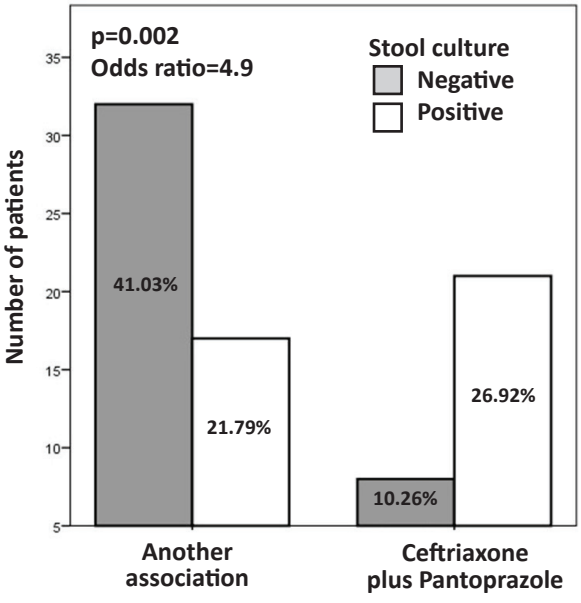

Fig. 3. Chi-square test for patients who received Ceftriaxone and Pantoprazole

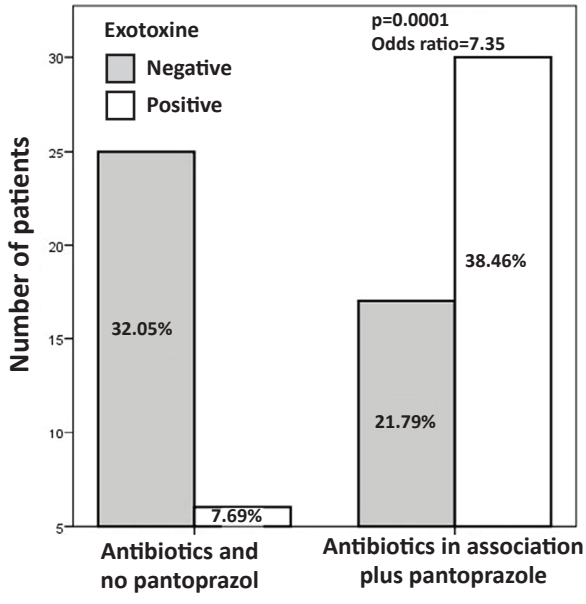

Fig. 4. Chi-square test of patients who received antibiotic and Pantoprazole

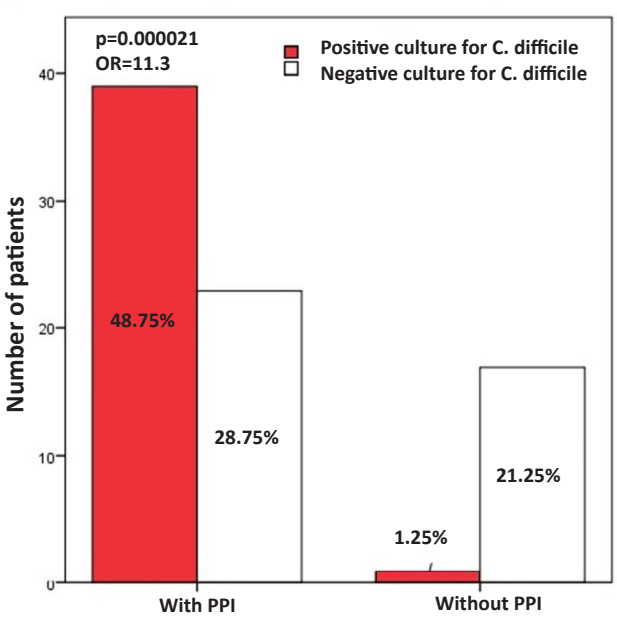

Fig. 5. Chi-square test for patients with PPI treatment and C.Difficile infection

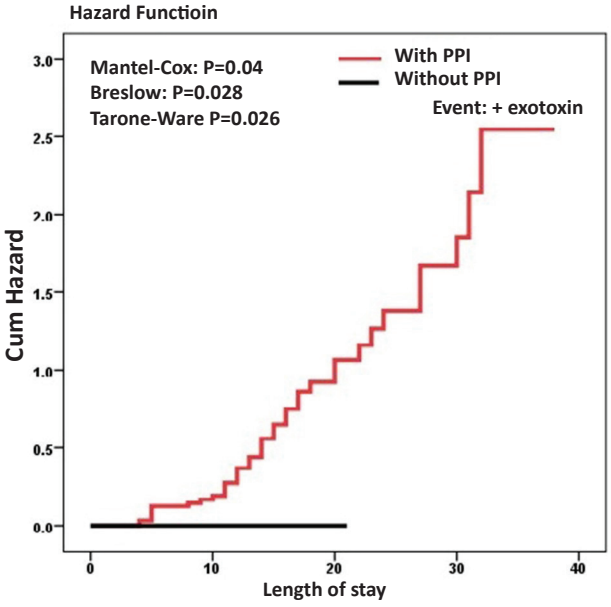

Fig. 6. Risk of patients with PPI treatment during the ICU stay

A function of the intestinal microflora is colonization resistance. The host's susceptibility to pathogens increases when this protective barrier is disrupted by antibiotics, medical or surgical treatment. [12]. It is the primary mechanism implicated in the occurrence of infectious diarrhoea and particularly in the development of CDI. In this study, the elevated patients number who underwent gastrointestinal surgery prior CDI could be explained by this evidence. Antibiotherapy alters normal gastrointestinal flora, facilitating the colonization and proliferation of CD. Clindamycin, fluoroquinolones, cephalosporins and β-lactam have been shown to be the antibiotics most often linked to CDI [1].

For assessment of long-term antibiotic therapy as a risk factor in CDI development, we use a model of logistic regression, with an overall percentage of 75%. The variable is considered the positive result for Clostridium difficile exotoxin. The model accuracy was 75%, and it did not discriminate whether the patients were receiving associated PPIs therapy or not.

The present study results indicate that ceftriaxone is most often associated with CDI, while carbapenems, metronidazole, and fluoroquinolones are also connected. We suggest that ceftriaxone administration is associated with Clostridium difficile infection. To see if PPIs associated therapy is involved in the development of CDI, we investigate the risk of combined antibiotic and PPI therapy. The combined antibiotic and PPI therapy is associated with CDI, increasing the risk of infection early in the administration period. This risk is minimal for the sole administration of ceftriaxone in the first five days. Therefore, the risk of infection is attributable to PPIs administration.

Pepin et al. [13] recommended a judicious use of antimicrobial agents in control of nosocomial CDI: sparing use of fluoroquinolones, substitution of intermediate-risk antibiotics with aminoglycosides when feasible and administration of trimethoprim-sulfamethoxazole to patients with urinary tract infections caused by a susceptible pathogen.

Gastric acidity is a major defence system against ingested pathogens. Elevated gastric pH secondary to PPIs administration is associated with infectious diarrhoea, including salmonellosis, campylobacteriosis, and cholera [14, 15]. CD spores are acid resistant while vegetative forms are susceptible to acidity. Any decreases in gastric acidity may facilitate conversion from spore to vegetative forms of CD in the upper gastrointestinal tract. Moreover, PPIs administration results in the impairment of leukocyte and other immune responses and antimicrobial properties [16]. Other mechanisms implied in CDI may be a PPI-induced increased gastrin-mediated effect on the colonic mucosa [17], an effect on immune function [18], or effects on the organism's toxin production [19]. The stronger acid suppression of PPIs enhances the risk of infections. This feature is less expressed in H_2RA activity, and also limits the reperfusion injury in animal models, possibly by

reducing oxidative stress after mucosal injury [20]. To see if PPIs administration is a risk factor for infection we use a logistic regression model. The model accuracy was 70%, with a significance of p=0.002. The present study shows that PPIs increases the risk of developing CDI seven-fold compared to H_2RA, regardless of the antibiotic used.

Those factors increasing the risk to CDI are, the severity of underlying illness, immunosuppression, multiple admissions per year, gastrointestinal tract surgery, the presence of one or more organ dysfunctions, as well as the exposure to or colonization with CD or the disruption of normal intestinal flora. Patient frailty, especially in elderly people, has been associated with CDI [21], which is supported by the present study where the mean patient age is >64 years.

Conclusions

This study indicates that there is no risk of developing CDI when antibiotics alone are administered in the first five days of medication. However, the co-administration of PPIs increased the risk of CDI in the first seventy-two hours.

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