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NOSOCOMIAL INFECTION WITH CLOSTRIDIUM DIFFICILE: ANALYSIS OF THE HOSPITALIZATION INDICATORS IN A LEVEL II B HOSPITAL IN ROMANIA

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Abstract: *The frequency of Clostridium difficile nosocomial infections (CDI) is on the rise and analyses of patient outcomes and hospitalization costs yield constantly changing results. It is difficult to assess the impact of CDI on hospital admission statistics, including costs, due to certain confounding factors such as the severity of the underlying disease, the overlap between the underlying disease and the CDI and the contribution of the risk factors to the onset of CDI. The present study shows that longer hospital stays for Clostridium difficile infected patients are due mainly to the serious underlying disease, and to a lesser extent to the CDI, and that these longer hospital stays are usually seen on surgical wards. Even though the contribution of the CDI to the extended hospital stay is modest, it can be further reduced through an early detection of the onset of infection.*

Key words: *Clostridium Difficile, Nosocomial Infections, Patient Discharge, Length of Stay*

1. Introduction

Clostridium difficile (CD) is a Gram-negative, anaerobic, spore-forming bacillus that colonizes the large intestine and releases two enterotoxins (TcdA and TcdB), which induce various types of colitis in susceptible patients. The CD strains express on their cell wall the glutamate dehydrogenase antigen (GDH), that is characteristic to all ribotypes [4]. CD also represents 1-3% of the intestinal microbiota of healthy people.

The presence of Clostridium difficile in medical facilities is almost ubiquitous, 25-55% of medical personnel being contaminated [5], [7]. CD spores can not only be found on the hands and stethoscopes of medical staff but also on telephones, bed linen and in bathrooms [19].

By definition, for a CD infection to be considered nosocomial, the onset of symptoms has to be at least 48 hours after

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admission into and up to 4 weeks after discharge from the hospital. Debate is still ongoing regarding the time period of 4 to 12 weeks after discharge due to the difficulty in confirming a hospital acquired infection at more than 4 weeks after discharge [24].

During the last decade, the incidence of CDI has increased 2-4 times, especially in elderly patients and in patients with prolonged hospital stays [17], reaching, according to the European Study Group for C. Difficile (ESGCD) up to 4.1 cases for every 10,000 patients [3], and in the USA, up to 15 cases for every 10,000 patients discharged in 2014 [21].

According to the epidemiological observations of the last years, CDI has become the main nosocomial infection, taking the lead in front of the methicillin-resistant Staphylococcus aureus [18] and increasing 4 folds the hospitalization costs for these patients [15]. Mortality due to the severe infection alone is 5%, but it can rise to 15-20% in patients with severe infection and associated pathology [8], [15].

The primary risk factors for the CDI include: male gender, age over 65 years, length of hospitalization and antibiotic treatment. The secondary risk factors include: comorbidities and underlying diseases such as chronic inflammation of the colon, HIV infection, malnutrition, neoplasms, diabetes etc. [23]. The risk factor that is unanimously acknowledged is the treatment with broad-spectrum antibiotics, which disrupt the normal flora of the intestines and allow the proliferation of the toxigenic Clostridium difficile. The use of any type of antibiotic may lead to CDI, the most common such antibiotics being clindamycin, ampicillin/amoxicillin, cephalosporins and fluoroquinolones [14]. Moreover, there are CDI occurrences triggered by administering metronidazole and vancomycin, two of the antibiotics of choice in the treatment of CDI [11].

Laboratory diagnosis relies on immunoenzymatic assays as screening tests for the GDH antigen in stool, to which can be added immunoenzymatic tests for the specific A and B enterotoxins, because such tests are cheap, fast and easy to perform, and have a sensitivity of 60% to 80%. By comparison, the PCR tests are more expensive and laborious, but far superior in detecting the BI/NAP1/027 strain, which is more susceptible to fidaxomicin than it is to vancomycin [7], [14].

2. Study Aims (Objectives)

To analyze the seasonal character as well as the incidence of CDI related to the total number of nosocomial infections and the distribution of CDI by hospital ward, as well as cumulatively for surgical versus medical wards, taking into account the cost increases due to longer hospital stay for the two types of wards (medical and surgical).

The study analyzed two risk factors related to CDI onset – antibiotic therapy prior to CDI onset and length of hospital stay up to CDI onset, as well as their relationship to the total hospital stay and patient outcome up to the time of hospital discharge.

We also analyzed the timeliness of CDI diagnosis, from onset of symptoms to initiation of specific antibiotic therapy.

3. Material and Methods

3.1. Design

In this study were included and analyzed all 104 patients admitted successively during the course of a year, between January 1st and December 31st, to one of the wards of Brasov County Emergency Clinical Hospital, who presented diarrheic stools during their hospital stay (with onset more than three days after their admission)

and had tested positive for the presence of the enterotoxins type A, B, or A/B in the stool. Brasov County Emergency Clinical Hospital is a level II b hospital, which according to the Romanian Ministry of Health means a hospital with a high level of competence and between 400 and 1200 beds, our hospital having currently a 910 bed capacity on 38 departments). The screening was done with a Clostridium specific chromatographic immunoassay for the rapid detection of the glutamate dehydrogenase antigen (NADAL® Clostridium Difficile GDH Rapid Test), followed by a second qualitative immunoassay for the specific toxins type A, B and A/B (NADAL® Clostridium Difficile Toxins A&B Test). The sensitivity and specificity of both tests is more than 99% without any cross-reactivity with other common gastrointestinal microorganisms (Campylobacter, Helicobacter, Salmonella, E. coli etc.).

Following the immunoenzymatic confirmation of the infection, the department for tracking of nosocomial infections was notified, and they completed the analysis chart for each case of nosocomial infection. Data was collected from this chart concerning the patient's age, gender, department, antibiotic classes used before the onset of CDI, discharge status and the hospitalization indicators (Total Length of Hospital Stay; Time from Admission to Onset of Symptoms; Time from Onset of Symptoms to Stool Sampling and Time from Onset of Symptoms to Patient's Discharge from the hospital). Comparisons were made with the department averages for Total Length of Hospital Stay recorded by the Brasov County Emergency Clinical Hospital during the same time period for all the different medical and surgical departments.

3.2. Statistical Analysis

The normality of the data was assessed using the nonparametric Kolmogorov-Smirnov test (K-S test) for one sample. Non-normal data was normalized using the Johnson transformation and used in the calculation of the Pearson coefficients for correlations and partial correlations (r, respectively rs), of the determination coefficients (R2) and of the t-student test. The parameters that could not be normalized were analyzed using nonparametric statistics (χ2-test). When comparing the averages, the variance equality assumption was assessed using the Levene's test. The averages of more than two groups were compared using ANOVA with Bonferroni correction.

Data processing software: SPSS 20, Minitab 17, Excel 2013.

4. Results

4.1. General Analysis

There were a total of 170 cases of nosocomial infection reported in this period by Brasov County Emergency Clinical Hospital, with a distribution by etiology shown in Figure 1.

Clostridium difficile was the infectious agent in 104 (61.2%) of these cases. The ratio of CD cases to the number of hospital admissions (38,392) yields an incidence of 27 CD cases for every 10,000 hospital admissions for the year.

The average patient age was 69.9 years old, SEM±1.25; [CI95% = 67.5; 72.4], with a fairly balanced gender distribution (male to female ratio = 1.16).

The age of 65 years old was considered the "cutoff age", above which there is an increased risk of a poor outcome and death indicated by the epidemiological observations. There were 34 patients under

65 years of age, and 70 patients over 65 years of age.

Even though the monthly distribution in Figure 2 suggests two frequency peaks, one during the spring months (March) and another in autumn (October), with the lowest values during the summer months, the observation is not statistically significant (KS-test; p=0.914).

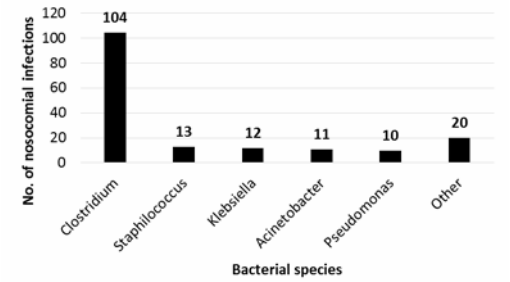

Fig. 1. *Distribution of nosocomial infections etiologies*

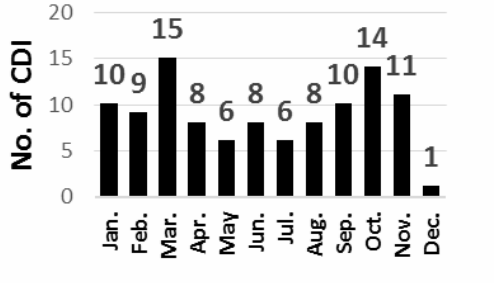

Fig. 2. *Seasonal distribution of cases*

The ratio of the CDI cases to the number of beds in each department is shown in Figure 3. The highest ratio was recorded in the Internal Medicine 1 Department (0.38), followed by the Hematology Department (0.32) and the Thoracic Surgery Department (0.30).

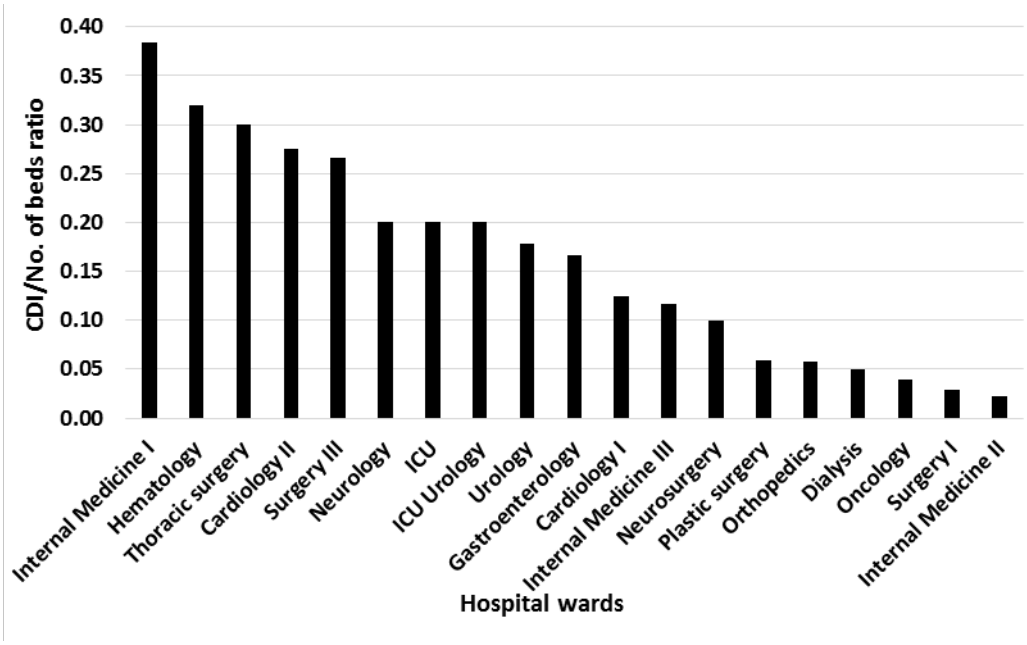

Fig. 3. *Frequency of CDI cases with respect to the number of beds in each department*

At the hospital level, 70 cases were reported on medical wards and 34 cases on surgical wards with average "CDI/department-bed" ratios of 0.17 and 0.15 respectively, and there was no statistically significant difference between the ratios (t=0.303 df=17 p=0.765).

Out of the 94 cases where information was available concerning the status of patients upon discharge from the hospital (Figure 4), 16 patients (17%) had a poor outcome, 12 patients (12.7%) died and 4 patients were discharged in an aggravated condition. There were no significant differences between patients with a favorable outcome and those with an unfavorable outcome in terms of the average age of the patient (70.5 and 67.3 years of age respectively), the "cutoff age" of 65, the gender, the ward on which the patient was treated (surgical or medical ward), or the average length of hospital stay.

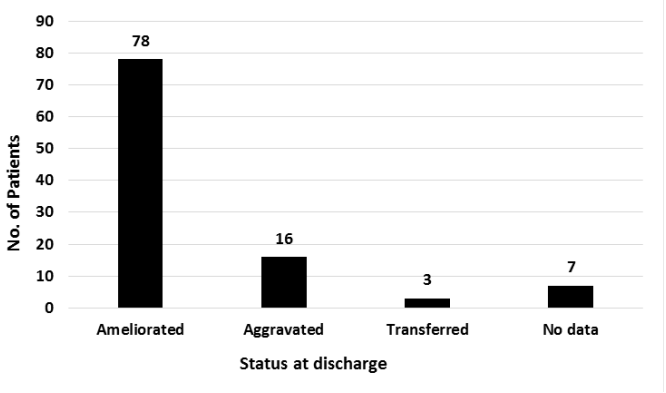

Fig. 4. *Status of the CD infected patients upon discharge*

Table 1

Comparisons between patients with a favourable outcome and those with an unfavourable outcome

Criteria	test	p
Average age	t=0.433;df=92	0.666
Less than 65 years/over 65 years	χ^2=1.012;df=1	0.384
Sex	χ^2=0.001;df=1	0.970
Medical wards/surgical wards	χ^2=1.407;df=1	0.236
Average no. of hospitalization days	t=0.099;df=92	0.921
Number of antibiotics before ICD	χ^2 =2.417 ; df=2 ;	0.299

4.2. Hospitalization Indicators Analysis

Average Length of Hospital Stay for the Clostridium difficile infected patients was 19.56 days [CI95% = 17.1;22; minimum 2 maximum 63], in comparison with the average Length of Hospital Stay of 6.43 days for the entire hospital.

The differences in the number of hospitalization days by department are shown in Table 2 and Figure 5.

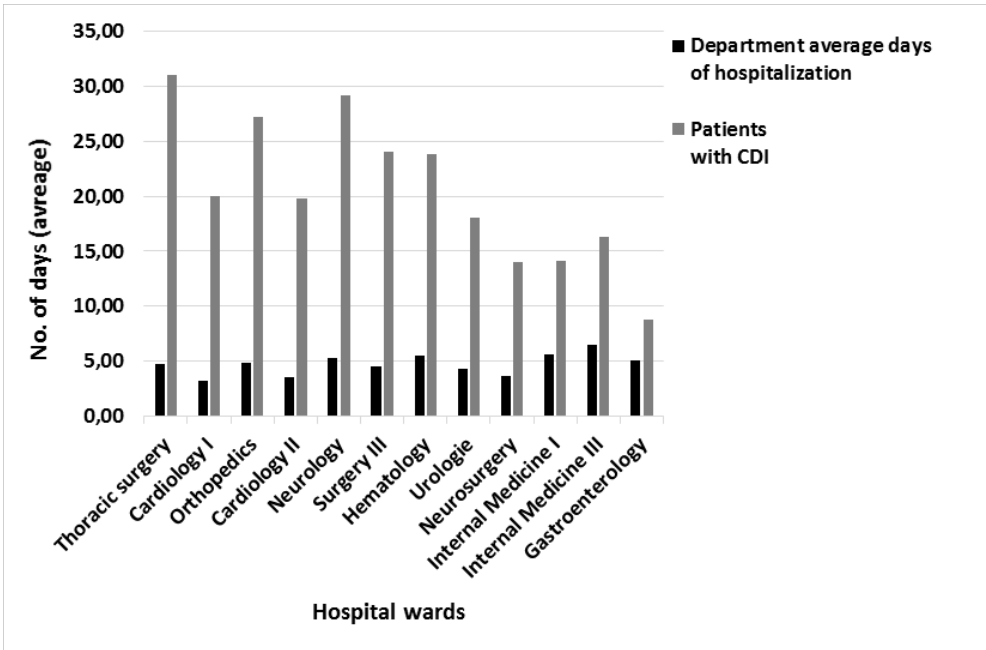

Fig. 5. *Department average number of days in hospital compared to the average length of hospital stay for the CD infected patients, by department*

Table 2

Analysis of the average length of hospital stay per

Wards	Deprtment average days of hospitalization	Patients with CDI	Average difference	Increase of hospitalization (fold increase)
Thoracic surgery	4.73	31	26.27	6.8
Cardiology I	3.21	20	16.79	6.2
Orthopedics	4.85	27.25	22.4	5.6
Cardiology II	3.57	19.8	16.23	5.5
Neurology	5.29	29.2	23.91	5.5
Surgery III	4.54	24	19.46	5.3
Hematology	5.5	23.87	18.37	4.3
Urologie	4.35	18	13.65	4.1
Neurosurgery	3.65	14	10.35	3.8
Internal Medicine I	5.66	14.16	8.5	2.5
Internal Medicine III	6.53	16.28	9.75	2.5
Gastroenterology	5.1	8.8	3.7	1.7
Average	**4.73**	**20.53**	**15.8**	**4.48**

The departments that reported only one or two cases of CDI were removed from the study. The CD infected patients had a 4.5 times longer hospital stay in comparison to the average length of hospital stay for the specific ward they were admitted to (Table 2).

The average Length of Hospital Stay was similar when comparing the patients with a favorable outcome (19.5 ±1.3 days) to those with an unfavourable outcome (21.4 ± 4.2 days) (t=0.099; df=92; p=0.921; Table 1). We calculated an average Length of Hospital Stay for all the medical departments and also an average Length of Hospital Stay for all the surgical departments. The average Length of Hospital Stay for the medical departments overall was significantly higher (by 1.17 days) than that for the surgical departments [CI95% =0.71;1.62; t=5.075 df=102 p<0.001]. However, the situation was reversed for the patients with CDI, the average Length of Hospital Stay for the surgical departments being 6.9 days longer than the average Length of Hospital Stay for the medical departments [CI95% =11.8;2 ; t=2.425 df=102 p<0.019]. Thus, we may assume that CDI is more costly for the surgical departments compared to the medical departments, at least in as far as the patient's extended stay in the hospital is concerned.

For 89 of the patients, the average Time from Admission to Onset of Symptoms was 11.87 days [CI95% =9.84-13.89; min 2 max 53, median = 9]. The remaining 15 patients had been recently discharged from the hospital and returned with diarrhea, which is why they were tested for CDI on their very first day back.

The average Length of Hospital Stay for the Treatment of CDI was 4.81 days [CI95% =4.11-5.63; min 1 max 28, median = 4] and it was considered from the time of receipt of a positive stool test result for CD toxins until the end of the specific anti-CD antibiotic treatment. The average Length of Hospital Stay for the Treatment of CDI comprises about 24.8% of the total number of hospitalization days, but it partially or totally overlaps the duration of treatment for the underlying disease.

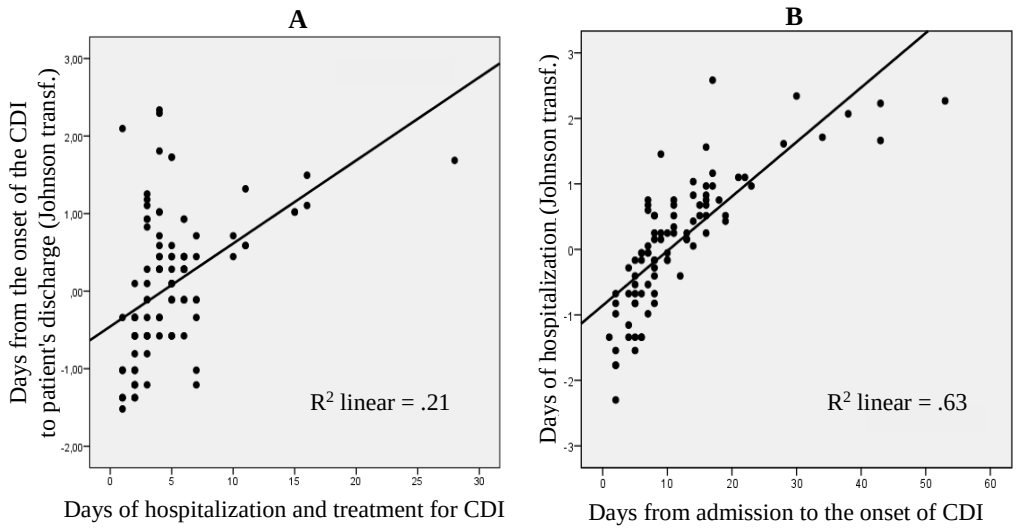

Fig. 6. *Correlation between the number of days from the onset of CDI to patient's discharge and the number of days of anti-CD treatment (number of hospitalization days for CDI) (A), and the correlation between the number of days from admission to the onset of CDI with the number of hospitalization days (B)*

There is a low power correlation (R2=0.21), approximately 20%, between the Time from Onset of Symptoms to Patient's Discharge and the Time Required for CDI Antibiotic Treatment (r=0.46; p < 0.001) (Figure 6 A). On the other hand, the Time from Admission to Onset of Symptoms strongly correlates (R2= 0.63) with the Total Length of Hospital Stay (r=0.794; p<0.001) (Figure 6 B). The statistical control of Time Required for CDI Antibiotic Treatment in analyzing the partial correlation between Time from Admission to Onset of Symptoms and Total Length of Hospital Stay shows that the influence of this indicator is practically null (rs=0.790; p<0.001, after controlling for the Time Required for CDI Antibiotic Treatment) in the relationship between these main indicators.

Stool sampling was done, on average, 2.44 days after the onset of symptoms. The cumulative percentage of patients tested was 55.8% in the first 24 hours, and 84.5% by day 4.

Analysis of the antibiotic treatment for the underlying disease (before the onset of CDI)

99 patients (95.2%) of 104 included in the study, received antibiotic treatment during their hospital stay, before the onset of the infection. 42 of these patients received antibiotic monotherapy, 39 received two antibiotics and the others received three or four antibiotics (Figure 7).

The classes of antibiotics used in monotherapy were: cephalosporins (20 patients on ceftriaxone and 4 on cefuroxime), quinolones (11 patients on ciprofloxacin), carbapenems (1 patient on imipenem and 1 on meropenem), azoles (2 patients on metronidazole), aminoglycosides (1 patient on gentamicin), rifamycin (1 patient on rifaximin) and glycopeptides (1 patient on vancomycin) (Figure 8).

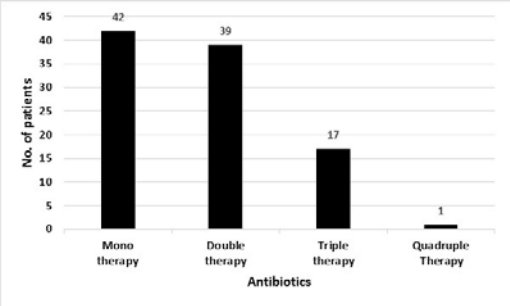

Fig. 7. *Type of antibiotic therapy administered before the onset of CDI*

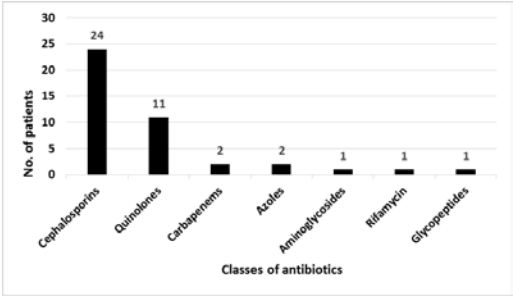

Fig. 8. *Classes of antibiotics administered before the onset of the CDI and the frequency of their administration*

In the treatment of 39 patients were associated two antibiotics. Cephalosporins were present in 26 of the combinations and quinolones were present in 9 of them. The most frequent combination was cephalosporin with aminoglycoside (13 cases), followed by cephalosporin with quinolone (12 cases).

The number of antibiotics administered before the onset of the CDI affects the Total Length of Hospital Stay (F=5.46; df=2; p=0.006) and the Time from Admission to Onset of Symptoms (F=5.59; df=2; p=0.005). The difference is statistically significant, especially between monotherapy and triple therapy. Thus, the total hospitalization period for patients

with triple therapy was 8.7 days longer (p=0.036) than that for patients with monotherapy, and the onset of the CDI symptoms was delayed by 9.4 days (p=0004) in patients with triple therapy in comparison with those undergoing monotherapy.

The status of the patient at discharge (improved or aggravated), was not affected by the number of antibiotics that were initially used for the underlying disease ($\chi 2$ =2.417; df=2; p=0,299) (Table 1).

5. Discussion

The spectrum of nosocomial infections is dominated by the CDI, comprising a little less than two thirds of the cases. The CDI frequency of 27 cases for every 10,000 discharged patients in 2014 was higher than the frequency of 15 cases for every 10,000 discharged patients reported for the same year in the USA [8]; however, an in-hospital mortality rate of 12.7% is at the lower limit of the 8-37% mortality range reported by various studies [4], [6], [9], [16]. If we add the patients that were discharged in a critical state (who are very likely to have subsequently passed away at home) the percentage goes up to 17%.

The seasonality of the CDI with maximums during the winter months and minimums in the summer has been described by many authors [2], [10], [13]. The alleged cause is the increase in antibiotic consumption during the cold months of the year due to an increase in the incidence of respiratory tract infections and exacerbations of COPD that require hospitalization. Even though the current study was conducted for only one year, it reflects this tendency. Nevertheless, for statistical confirmation purposes, data must be recorded for several consecutive years.

The primary risk factors for CDI, such as male gender, age over 65 years, Total Length of Hospital Stay, number of antibiotics administered before the onset of the CDI[23], did not influence the subsequent, favorable or unfavorable, outcome of the patients who went on to develop CDI (Table 1).

The Time from Onset of Symptoms to Stool Sampling is of approximately two and a half days, except for the patients suspected of nosocomial CDI who returned for admission and for whom the stool sample was collected on the first day. Said period is considered long for an in-patient, for whom the suspicion of CDI should be intuited faster, at the first signs of diarrhea.

The prospective study conducted in 2015 by Abdelsattar, which analyzes postoperative Clostridium difficile infections, shows an increase in the average postoperative hospitalization period from 4.5 days for the general average to 13.7 days (a 3-fold increase) for the postoperative CDI cases, the CDI incidence being independently associated with the hospitalization period [1]. Data from our study shows a 5-fold increase in the hospitalization period on surgical wards and a 2.5 fold increase on the medical wards, contributing to an increase in costs, especially for the surgical departments, in as far as the length of the hospital stay is concerned.

The fact that an extended hospitalization period increases the risk of developing a Clostridium difficile infection [1] is well known. However, it is difficult to quantify how much CDI itself increases the hospitalization period, since there arise confounding factors when we take into account the severe underlying disease requiring extended hospitalization, the risk of CDI increasing as the hospitalization period lengthens and the simultaneous treatment of the coexisting pathologies. The strong correlation between the Time from Admission to Onset of Symptoms and the Total Length of Hospital Stay suggests that the increase in the length of

stay in the hospital is mainly due to the more severe underlying disease and not to the subsequent complication in the form of the Clostridium difficile infection. This observation is supported by the following: a) the hospitalization period for the patients with triple therapy is significantly longer compared to the hospitalization period for patients with monotherapy, meaning longer hospital stays for critical patients who require treatment with more than one antibiotic from the moment they are admitted; b) the absence of statistical significance of the Time Required for CDI Antibiotic Treatment in the relationship "Time from Onset of Symptoms to Patient's Discharge /Total Length of Hospital Stay" and c) CDI risk factors do not influence the subsequent patient outcome.

It is estimated that CDI increases hospitalization costs 4-fold [15]. In our study, the Time Required for CDI Antibiotic Treatment represents almost a quarter of the total number of hospitalization days (24.8%); however, confounding factors make it difficult to quantify the CDI intrinsic contribution to the increase in costs resulted from extended hospitalization.

The injudicious prescription of medicine can increase the risk of CDI seeing that more than half of the admitted patients received at least one antibiotic, with the studies showing that in 30-50% of the cases the prescription of said antibiotic was incorrect or useless.[5] Our study suggests that the prevention of CDI in critical patients is a difficult undertaking because their underlying disease takes precedence from a treatment point of view, and such treatment often requires double or triple antibiotic therapy. However, in these cases, physicians must carefully consider the association of cephalosporins with quinolones or of cephalosporins with aminoglycosides. Furthermore, physicians must never forget about the rare possibility that the anti-CD antibiotics of choice, such as metronidazole and vancomycin, can precipitate the onset of CDI.[11,23] We found this reflected in our study, where 3 of the included patients have received anti-CD antibiotics before the onset of CDI.

6. Conclusions

The risk factors associated with the onset of CDI do not influence the subsequent course of the disease until patient's discharge.

An earlier recognition of the onset of CDI is necessary.

The greatest contribution to the increase in the Total Length of Hospital Stay compared to the department averages is the severity of the initial underlying disease. Even though the CDI extends the hospitalization period, the contribution of the actual infection represents only 20% of the weight of all other potential causes.

CDI increases hospitalization costs by extending the hospitalization period, especially in the surgical departments that have a smaller overall average of the Total Length of Hospital Stay compared to the medical departments.

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