FACTORS THAT IMPACT THE RISK OF DEATH IN CLOSTRIDIUM DIFFICILE INFECTION

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ABSTRACT

Introduction*: The purpose of the current study is to determine the impact of clinical and paraclinical factors on death rate after an episode of Clostridium difficile infection (CDI).*

Materials and methods: *The study was performed on 706 patients admitted to the "St. Parascheva" Clinic Hospital of Infectious Diseases Galati, between 1.01.2017÷31.12.2018 .*

Results: *The results of the study show that the following factors significantly influence the death rate after a CDI episode: leukocytes - an increase by 1000 of them increases the risk of death 1.06 times; albumin - an increase of 1 g/dl decreases approximately 5 times the risk of death; hemoglobin value - an increase of 1 g/dl decreases the risk of death by 20%; sodium - an increase of 1 mEq/L of blood sodium level decreases by 5% the risk of death; potassium - an increase of 1 mEq/L of blood potassium level decreases the risk of death by 28%; creatinine - an increase in serum creatinine by 1 mg/dl increases the risk of death by 30%; ATLAS score - an increase of the ATLAS score by 1 unit, increases the risk of death by 1.5 times and ascites - patients with ascites have a risk of death about 4 times higher than those without ascites.*

Conclusion: *The influence of comorbidities on the risk of death at 30 days from the episode of CDI and at 6 months after the episode of CDI is very high. Clostridium difficile infection is only a potentially aggravating or precipitating factor, the primary cause of death being the basic disease. The onset of CDI can be considered a predictive factor of death in these patients with multiple comorbidities.*

Keywords: *Clostridium difficile, death, risk factor, comorbidities.*

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Introduction

The infection with Clostridium difficile (CDI) is a pathology predominantly associated with healthcare, which can be prevented by hygiene measures and revision of antibiotic guidelines, which affects especially hosts with multiple comorbidities, which may have mild and severe clinical forms with high death rates. Clostridium difficile infection involves various clinical forms, from asymptomatic forms, to diarrhea with mucus and blood stools to severe forms with toxic megacolon or acute abdomen. The severity of the disease episode depends on the microbial ribotype involved and the host's susceptibility. The most widespread type of Clostridium difficile (CD) in the United States was ribotype 027 (28.4%), in a CDC study, in 2009, and in England it had a prevalence of 55%, in 2007[(1)].

Some studies in Romania show that the main circulating strain is ribotype 027[(2, 3)]. The high percentage of strains 027 identified by the own study - 93.61%, draws attention to the possibility of case evolution towards severe forms with reserved prognosis[(4-7)]. There have been described risk factors for both the onset of Clostridium difficile infection and death from this infection.

Risk factors for triggering the episode of CDI

Antibiotic therapy is the most important modifiable risk factor for CDI. The other risk factors incriminated in triggering the episode of CDI are: age over 65 years, contact with medical care units, cancer chemotherapy (by neutropenia-induced immunosuppression), gastrointestinal surgery, feeding on the nasogastric tube, upper or lower digestive endoscopy, patient's comorbidities (chronic or disabling diseases accompanied by immunosuppression)[8-15].

The classes of antibiotic considered high risk for CDI (odds ratio 5 or higher) are: clindamycin, fluoroquinolones, cephalosporins, aztreonam and carbapenems. The antibiotic classes considered moderate risk for CDI (odds ratio 1-5) are: macrolides, sulfonamides/trimethoprim and penicillins[16].

Post-antibiotic gut microbiota disorder is long-lasting, and the risk of CDI is increased both during therapy and 3 months after cessation of therapy, the highest risk of CDI (7-10 times increase) is in the first month after antibiotic exposure[17]. The risk of CDI increases with the duration of antibiotic therapy and with exposure to several antibiotics[18-20].

The use of proton pump inhibitors (PPI) and H2 receptor blockers has a potential controversial risk. Although a number of clinical studies have shown an epidemiological association between their use and the occurrence of CDI[21-26] and a meta-analysis of gastroenterologists from Iasi-Romania provides evidence that the use of PPIs is associated with an increased risk for the development of CDI, however, other prospective high quality studies are needed to assess whether this combination is causal[27].

Risk factors for mortality through CDI

Risk factors for mortality from CDI are considered: age, comorbidities, hypoalbuminemia, leukocytosis, acute renal failure and ribotype 027 infection[28-30].

Materials and methods

A prospective, observational, actively controlled study was performed on 706 patients admitted to the "St. Parascheva" Clinic Hospital of Infectious Diseases Galati between 1.01.2017÷31.12.2018 with the diagnosis of Clostridium difficile Infection.

Criteria for inclusion in the study were:

• Adults with unformed stools, over 3 in the last 24 hours, with a consistency of 6-7 on the Bristol scale[31] and toxins of Clostridium difficile A or B or A and B positive;

• Patients who have written informed consent for participation in the study, staff in full knowledge.

Exclusion criteria from the study were:

• Unconscious patients or inability to sign informed consent;

• Patients who refused to participate in the study;

• Pregnant or breastfeeding women;

• Patients under 18 years; patients who had extreme values ("outliers") in the usual laboratory tests (leukocytes, hemoglobin, serum albumin, ionogram, serum creatinine).

Patients were monitored during the hospitalization period and at one month, 2 months and 6 months after discharge, they were evaluated by telephone or in hospital.

Study sublots

The 706 patients were divided into 2 groups: group A (N = 553) consisted of patients with healthcare-associated infection, while group B (N = 153) consisted of patients with infection of indefinite and community source. It is worth mentioning that not all patients have complete data available. The endpoint of the study was the number of deaths.

For statistical analysis, R program, version 3.5.3 (c) R Core Team (2019), R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/[32]. Statistical analysis of the demographic data was performed on the group of patients with CDI associated with healthcare (group A) compared to the one with CDI of community and indeterminate origin (group B). The presentation is in Mean ± D.S (standard deviation) for continuous variables and in absolute frequency (relative frequency) for categorical variables, the test used in the inferential analysis being specified for each variable.

It is observed that there were non-homogeneous variables between the 2 groups (there were differences with statistical significance between the 2 groups). In order to analyze the endpoint, it was decided to "mitigate" these differences, using a propensity score. The propensity score was calculated using the R twang package version 1.5: Toolkit for Weighting and Analysis of Nonequivalent Groups (33), the propensity score being calculated using an ATE (average treatment effect) algorithm, view that it was possible for patients with community disease to have the same comorbidities as those with nosocomial disease.

For the calculation of the score were taken into account the variables that in the tests revealed dif-

ferences with statistical significance, apart from the Charlson score, because it depends on all the compared variables and not on all the comparison tests the differences were with statistical significance. The propensity score calculation algorithm was a "general boosting" type, based on regression trees and comprised 10,000 iterations, to ensure that the attenuation by propensity score was optimal.

Results

The frequency of deaths was 18.13% (128 out of 706 patients), group A was 20.43% (113 out of 553 patients), and group B was 9.80% (15 out of 153 patients), at 6 months after the CDI episode. The death rate at 30 days from the CDI episode was 10.48% in the total group, 11.93% in the group A and 5.23% in the group B. Knowing that the 30-day death rate in the US epidemic from 2010-2011 was 6.46%, we can say that the group with healthcare-associated infections had a increased mortality at the 30 days from the CDI episode[34-38].

The mean age was statistically significantly higher in the group with infections associated with healthcare. In this group the average age (68.02 years) is above the risk age for ICD (65 years). Patients with community infections are younger (mean age = 59.78 years), without being in the risk zone.

We have analyzed the type of infection (nosocomial vs. community), making a gross analysis for the beginning (the propensity score calculated previously was not taken into account): OR = odds ratio; 95% CI = 95% confidence interval. The analysis suggests that the risk of death in patients with nosocomial type infection is 2.43 (IC95%-1.49 to 4.13) times higher than in patients with community infection, the effect being statistically significant (p=0.0005), but this result is influenced by the inhomogeneities regarding comorbidities between the 2 categories of patients. The attenuated analysis using the propensity score reveals that the type of case does not seem to influence the risk of death (p=0.234), comorbidities appearing to play a more important role than the type of infection. To investigate the role of comorbidities in the risk of death, simple univariate binary logistic regression with independent variable Charlson score, was used[39]. From the analysis it is observed that an increase of 1 unit of the Charlson score is associated with an increase of 1.26 (IC95%-1.15 to 1.40) times the risk of death at 30 days from the episode of CDI (effect with statistical significance, p<0.01), while an increase with 1 unit of the Charlson score is associated with a 1.29 (IC95%-1.19 to 1.40) -fold increase in the risk of death at 6 months from the episode of CDI (effect, also with statistical significance, p<0.001). The results are similar, the influence of comorbidities on the risk of death at 30 days from the episode of CDI and at 6 months after the episode of CDI is very high (Figure 1).

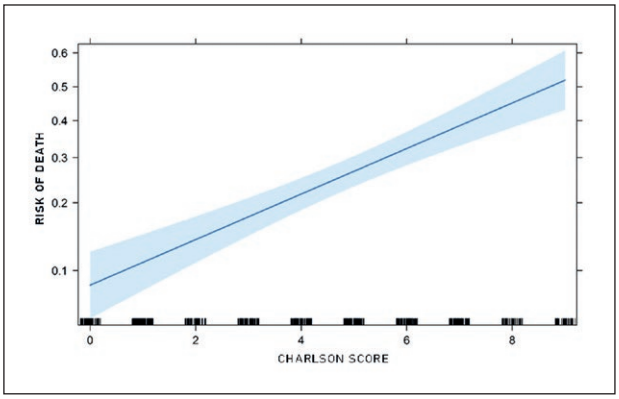

Figure 1: The influence of the Charlson score on the risk of death.

Because in patients of our study, comorbidities, as quantified with the Charlson score, play a major role in the risk of death, another analysis considered the Charlson score for each independent variable, the model being that of multiple univariate binary logistic regression (2 independent variables in the analysis). The analysis is shown in table 1.

Variable	*Coefficient*	*p Value*	*OR [IC95%]*
The number of leukocytes (thousands)	0.06	< 0.0001	1.06 [1.03 to 1.09]
Albumin	-1.66	< 0.0001	0.18 [0.12 to 0.28]
Hemoblobin	-0.20	< 0.0001	0.81 [0.74 to 0.89]
Na	-0.04	0.0130	0.95 [0.91 to 0.98]
K	-0.32	0.0318	0.72 [0.53 to 0.96]
Creatinine	0.28	0.006	1.32 [1.08 to 1.63]
ATLAS score	0.40	< 0.0001	1.49 [1.32 to 1.69]
Ascites **Yes** **No**	REFERENCE -1.44	- < 0.0001	- 0.23 [0.13 to 0.39]

Table 1: Influence of clinical and paraclinical parameters on the risk of death.

Analyzing table 1, it can be stated that the following parameters influence the risk of death, in the patients from our study: the number of leukocytes - an increase by 1000 of them increases the risk of death 1.06 times; albumin - an increase of 1 unit of measure decreases approximately 5 times the risk of death; hemoglobin value - an increase of 1 unit decreases the risk of death by 20%; an increase of 1 unit of plasma Na decreases by 5% the risk of death;

an increase of 1 unit of serum K decreases the risk of death by 28%; an increase in serum creatinine by 1 unit increases the risk of death by 30%; an increase of the ATLAS score by 1 unit, increases the risk of death by 1.5 times (40); patients with ascites have a risk of death about 4 times higher than those without ascites. Multiple univariate binary logistic regression was used, using besides the Charlson comorbidity score (kept in permanent model), the independent variables for which the value p was statistically significant (eg<0.05), the final model in table 2 being built on the basis of an retrograde selection algorithm ("backward selection").

Variable	*Coefficient*	*p Value*	*OR [IC95%]*
Albumin	-1.50	< 0.0001	0.22 [0.14 to 0.33]
Creatinine	0.21	0.0658	1.24 [0.98 to 1.57]
Ascites Yes	REFERENCE	-	-
No	-0.92	0.0080	0.39 [0.19 to 0.78]
Charlson Score	0.12	0.0136	1.12 [1.02 to 1.24]

Table 2: Influence of serum albumin and creatinine, presence of ascites and the Charlson score on the risk of death.

Discussion

The factors that significantly influence the death rate after a CDI episode were: the number of leukocytes, seric albumin, hemoglobin value, serum Na, serum K, serum creatinine, ATLAS and CHARLSON score, ascites. Severity of the disease episode and the patient's comorbidities influence the post-CDI death rate. The management of a patient with CDI must include the evaluation of the number of leukocytes, serum albumin, hemoglobin, sodium and potassium, creatinine, as well as the calculation of CHARLSON and ATLAS scores, as well as the diagnosis of ascites and the treatment led after severity of these parameters.

The presence of comorbidities and their severity greatly impact the death rate after an episode of CDI. It can be considered that the occurrence of the CDI episode is a predictive factor of death in a patient with multiple comorbidities. Also, the episode of CDI can be considered a factor of aggravation of the general condition of a patient with multiple comorbidities and acceleration of death but the main cause of death remains the initial comorbidity, chronic disabling disease that causes the patient's immunocompromised status.

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