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Clostridium difficile infection in patients with chronic hepatic disease

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ABSTRACT

Clostridium difficile infection (CDI) associates in the spectrum of comorbidities, more and more often, chronic toxic metabolic or viral hepatic diseases. Patients with chronic hepatic diseases have more severe episodes of CDI with poorer prognosis than episodes of CDI that have occurred in patients with other comorbidities. The measures of prophylaxis and treatment of CDI in these patients require particularizations according to the risk factors and the clinical-evolutionary specificity of these patients. The present study aims to identify the main risk factors of these patients for CDI, as well as to evaluate the severity of the episodes of CDI, the rate of recurrence and death in these patients, compared to those without liver disease.

Keywords: *Clostridium difficile*, chronic liver disease, prophylaxis, prognosis

INTRODUCTION

Case studies of patients with chronic liver disease and acute episodes of *Clostridium difficile* infection have been reported in the literature since 2007 [1,2,3,4].

Subsequent studies have suggested that chronic liver disease is a risk factor for CDI and the onset of this infection in a chronic liver patient increases the costs of medical care and its death rate [5,6,7].

This paper aims to identify the features of CDI in patients with chronic liver disease from an epidemiological, clinical and therapeutic point of view.

Clostridium difficile (CD) is the most important pathogen of postantibiotic gastroenteritis. CD infection may develop clinically from asymptomatic portage forms and mild acute gastroenteritis from severe forms of pseudomembranous colitis, ileus, and toxic megacolon. If the CDI was initially considered a healthcare associated infection, it is now noticeable its extension in the community and the increase in the number of cases of community origin. The epidemic in the United States, Canada and Europe, from 2010-2011 was due to the emergence of the hypervirulent CD strain, ribotype 027, by a genetic mutation that determined the resistance to fluoroquinolones, the secretion of a new toxin, the increased quantitative secretion of toxins and the capacity increased to form spores, compared to the historical strain [8]. The structure of the microbial DNA of the CD, with multiple transposomes, allows a great genetic variability to the bacterium, which may determine in the future the selection of other strains with high virulence, capable of new epidemics [9].

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Patients receptive to CDI have: alteration of intestinal microbiota after antibiotic and immunosuppressant, compromise of mucosal barriers after surgery, trauma, tumor proliferation, ischemia or necrosis, as well as decrease of the general resistance of the body, caused by age, alcoholism, diabetes, alcoholism, diabetes, angiopathies.

The association of CDI in patients with chronic liver disease (CLD) can be explained by the immunosuppression and inflammation induced liver disfunction. Chronic hepatitis involves a massive inflammatory infiltrate into the liver, which results in the activation of Kupfer cells and the release of pro-inflammatory cytokines [10]. As a result, there is a depletion of antioxidants and a chronic release of oxygen free radicals, which causes disruption of natural hepatic immunity [11,12]. In addition, immunosupression of patients with liver cirrhosis or autoimmune hepatitis could be amplified by malnutrition or immunosuppressant drugs, including corticosteroids.

Clostridium difficile infection occurs more frequently in the hepatology sections, whereas in other sections, the association of chronic hepatopathies with CDI is mentioned in 0.9% of the outpatients in the hepatology, compared with 0.29% in the outpatients in other sections [13].

A multicenter Canadian study reports 62/1,430 (4%) cases of CDI / CLD [14] and one in the United States 1,165 / 59,385 (2%) CDI / cirrhosis [6]. The percentage of cases of CDI of community origin described in clinical studies in cirrhotic patients varies between 11% (20.21) and 13% [6].

Risk factors for CDI of patients with CLD could be the advanced age, nosocomial exposure through periodic assessments for the CDL and hospitalizations for its decompensations, endoscopic examinations for monitoring of esophageal varices, antibiotic therapies for various infections caused by immunosuppression or proton pump inhibitor therapies for hyperacidity-induced disorders associated with hepatopathies.

Considering the imbalances of commensal microflora found in patients with cirrhosis, asymptomatic CD carrige can reach 20% [15]. Clinical studies in Asia in groups of patients with postviral hepatic cirrhosis showed significantly reduced levels of *Bifidobacterium spp.* [16,17] and *Lactobacillus spp*. in patients with alchool-related hepatitis [18]. Other supplementary risk factors for CD in cirrhotic patients are the delayed bowel motility and increased intestinal pH [16]. Hypogamaglobulinemia, as well as their immunosuppressive medication are found in patients with autoimmune hepatitis and after liver transplantation.

Clinical manifestations of CDI in the patient with CLD include fever and abdominal pain more common than in the patient with CDI without CLD [6]. Cases of extra-intestinal CDI have been reported in patients with CLD [6], including splenic and hepatic abscesses [19 20] and bacterial peritonitis in patients with ascites in which C. difficile was cultured from peritoneal fluid [19,21,22].

The recurrence rate of CDI ranges from 15-35% in various clinical studies [2,3,23,24].

The post-CDI death rate is higher in patients with chronic liver disease [2]. The severe progression of CDI related to CLD was assessed by therate of admission to an intensive care unit and the need for surgery (colectomy) [14, 25].

According to a large clinical study [6] they were compared a group of 1,165 patients with viral liver cirrhosis and CDI with a group of 58,220 patients with CDI alone. The death rates were 13.8% versus 9.6%, with average hospitalization time 14.4 days vs. 12.7 days and average hospitalization costs 79,351 USD versus 57,708 USD. This study also demonstrated that the risk of mortality associated with CDI was similar to those of other complications of cirrhosis, such as hepatic encephalopathy (OR 1.94, 95% CI 1.83-2.06), variceal bleeding (OR 1.63, 95% CI 1.49-1.78), spontaneous bacterial peritonitis (OR 1.98, 95% CI 1.45-2.70) and ascites (OR 1.30, 95% CI 1.22-1.38), which highlights the importance of CDI in this patient population.

MATERIAL AND METHOD

A prospective, observational, actively controlled study was carried out on a batch of 715 adult patients admitted to the Clinical Hospital of Infectious Diseases "St. Cuvioasa Parascheva" Galati, in the period 1.01.2017 ÷ 31.12.2018 with infection with *Clostridium difficile* (CDI). There are 119 cases (16.6%) with chronic liver diseases and 596 (83.3%) with CDI alone. The chronic liver diseases included 48.73% chronic hepatitis, 41.17%, liver

cirrhosis, 5.88% liver steatosis and 4.20% liver cancer (figure 1).

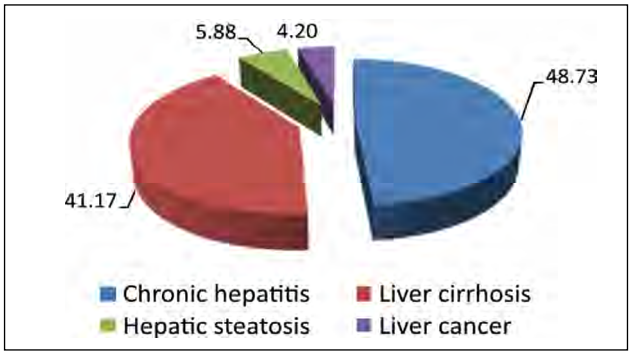

FIGURE 1. *CDI-associated liver disease*

The group of 119 patients with *Clostridium difficile* and chronic liver disease (CDI+LCD+) was compared with the group of 596 patients with CCI alone (CDI+CLD-). The demographic data, the general comorbidity profile, the severity of the disease episode, quantified by the ATLAS score, length of hospitalization, number of days of specific antibiotic treatment until the normalization of the stool and duration of antibiotic treatment. The prognostic comorbidities Charlson score was calculated based on the medical history. The criteria for stool normalization are maximum 2 stools daily, with 1-4 consistency by Bristol scale, at least 48 hours [26].

The prognosis of CDI episode was quantified by the recurrence rates, re-infection rates and the death rates, comared in CDI+CLD+ and CDI+CLD-. Reappearance of the symptoms with more than 3 stools, with 6-7 consistency by the Bristol scale in the last 24 hours and toxins A and / or B positive for CD, was defined as recurrence in the first 8 weeks and as re-infection in weeks 9-24 from the clinical resolution of the CDI episode.

The statistical analysis used the MedCalc program, version 15.8. The numeric data (age, the length of hospitalization, the days number until stool normalization and the length of antibiotic treatment, were assessed by descriptive statistics and by Pearson, $\chi 2$, Student-t test correlation methods, with $p < 0.05$ significance level.

RESULTS

The etiology of chronic liver disease was predominantly metabolic toxicity in 55.46%, following the viral etiology, specified as 25.21% hepatitis C virus, 16.81% hepatitis B virus and 2.52% association of hepatitis B and D viruses (figure 2).

The community origin (C) of cases was 21.84% in the CDI+CLD+ group 19.79%, CDI+LCD- group, over the national average of CDI in 2018 (19%) [27]. These data, and the reports of clinical studies on association of CDI and CLD, ranging between 11% and 13% [6,28,29], suggest the spread of infection in the community (figure 3).

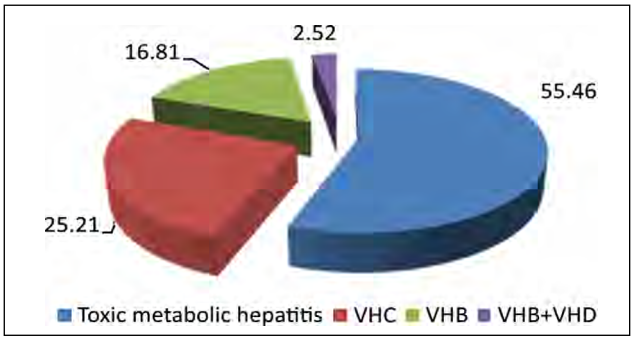

FIGURE 2. *Etiology of hepatic diseases associated with CDI*

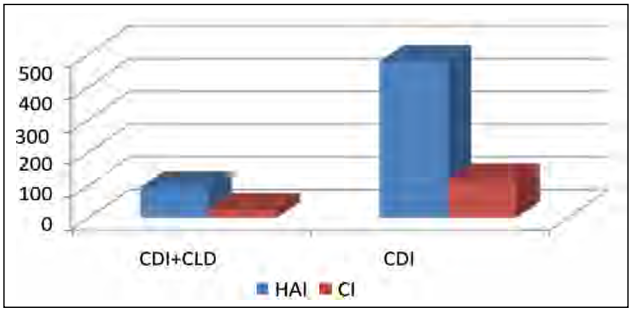

FIGURE 3. *Origin of CDI cases: healthcare associated infection (HAI); community origin infection (CI)*

The characteristics of the lot with CDI and CLD, as well as the one with CDI only and their statistical correlation are presented in table 1 and 2.

Demographic characters

The average age of all patiens with CDI was over 65 years old, with significant difference between the two groups ($p = 0.029$) and younger age of patients with CLD (63.3 vs. 66.5) (Table 1). Males were prevalent in the group with CLD, while females are more often with CDI alone ($p < 0.001$).

The urban living environment prevails in both groups, but the percentage of patients from rural is higher in the in the CLD group. The higher share of the rural environment, as the male ratio in the group with CLD may be related to the fact that the alco-

TABLE 1. *Numeric correlations of CDI characteristics with CLD or not*

	CDI+CLD+ (N 1 = 119)			CDI+CLD- (N 2 = 596)			T-t p	95% CI
	Av.	SDev	Max; Min	Av.	SDev	Max; Min		
Age(years old)	63.63	13.29	89;21	66.55	15.70	95;18	0.029	-5.742; -0.305
Hospitalization length (days)	8.22	8	43; 1	8.11	3.58	28;1	0.820	-0.829; 1.044
Number of days until stool normalization	4.41	2.98	17; 1	4.75	2.87	22; 1	0.256	0.249; -0.929
Treatment duration (days)	10.13	3.19	24; 1	10.27	3.97	65;1	0.668	-0.805; 0.517

Legend: Av = Average; SDev = Standard Deviation; Max = Maximum Value; Min = Minimum value; T-t = Student Test (t) for differences between means; CI = confidence interval

holic hepatitis are predominate in the study group. Alcohol use is more frequent in the rural area, due to the households tradition of alcohol manufacture and to consume it in the family, particular in Romanian rural area.

Analysis of risk factors

Patients with hepatopathies are younger when developing the episode of CDI than those with other pathologies associated with CDI. The average age of both groups falls in the first degree of severity of the Atlas score (60-70 years) [30].

The chronic consumption of proton pump inhibitors (PPI), especially by cirrhotic patients due to the prophylaxis or the treatment of the relatively frequent upper digestive haemorrhages in them, is statistically significantly higher in the group with CDI and CLD compared with the group with CDI only.

The low levels of gastric acidity, the consequence of the chronic consumption of PPI correlates with the increased levels of asymptomatic portage observed in the cirrhotic patients and may be one of the primary risk factors in triggering the CDI in this category of patients. This result opens the prospect to further, more detailed studies on the association of low levels of gastric acidity with asymptomatic CD carriers and its impact on the development of CDI in immunosuppressed patients. The endoscopic procedures done for diagnostic or therapeutic purpose, previous the CDI episode, had represented a high risk of direct inoculation of bacteria on the digestive tract and were significant more frequent in patients with CLD.

Antibiotic consumption before the onset and the abdominal surgery during the last 8 weeks before the onset of CDI, had similar weights in the two groups.

The comorbidities of patients with CDI, as measured by the Charlson score [31], had similar weights in both study groups.

Analysis of the severity of the episode and the prognosis of CDI

The severity of the CDI episode, quantified by the ATLAS score [30], are not influenced by the association of CLD. Among the laboratory criteria of ATLAS score at the onset of CDI, the levels of serum leukocytes and serum creatinine were comparable in the two groups, while the level of serum albumin was statistically significant lower in the group with hepatopathies, due to the specific decreased synthesis during the advanced liver disease.

The duration of hospitalization, as well as the number of days of antibiotic needed until the normalization of the stool and the number of days of specific antibiotic treatment had similar weights in both study groups (Table 1).

The re-infection rate was not influenced by the CLD association, mean while the recurrence rate was significant higher in patients with liver injuries ($p = 0.035$).

The high rate of deaths occurring in the next 6 months from the CDI episode was correlated with CLD association, but the difference of mortality during the next 30 days from CDI was not significant.

DISCUSSIONS

The comparative study of patients with CDI and chronic hepatopathy compared with those with other associated comorbidities identifies risk factors with significant weight in the first group, as op-

TABLE 2. *Characteristics of categorial variables of the patients with CDI and statistic analysis of groups associated or not with CLD*

	CDI+CLD+ N = 119		CDI+CLD- N = 596		OR	OR 95%CI	X2 Test p
	n	%	n	%			
Sex							
Female	49	41.17	347	58.22	0,502	0,338; 0,745	
Male	70	58.82	249	41.77			***<0.001***
Living Area							
Urban	69	57.98	412	69.12	0,616	0,412; 0,920	***<0.001***
Rural	50	42.01	184	30.77			
Charlson Score 0-3	55	46.22	252	42.28	1.459	0.889; 2.196	0,145
4-6	37	31.09	237	39.77	0.618	0.359; 1.064	0.083
7-14	27	22.69	107	17.95			
Antibiotics before CDI onset							
Yes	85	77.51	462	71.4	0.725	0.466; 1.126	0.152
No	34	22.48	134	28.57			
PPI before CDI onset							
Yes	57	47.89	145	24.32	2.859	1.926; 4.244	***<0.001***
No	62	52.10	451	75.67			
Endoscopy before CDI onset							
Yes	8	6.72	21	3.52	1.973	0.864; 4.502	***<0.001***
No	111	93.27	575	96,47			
Abdominal Surgery							
Yes	8	6.72	62	10.47	0.616	0.288; 1.314	0.106
No	111	93.27	530	89.52			
ATLAS Score							
0-3	94	78.99	497	83.38	1.335	0.818; 2.178	0.247
4-9	25	21.00	99	16.61			
Leucocytes >15000/mm^3							
Yes	22	18.45	110	18.48	0.993	0.603; 1.663	1.00
No	97	81.54	486	81.51			
Creatinine >1.5 mg/dL							
Yes	27	23.15	142	26.05	1.169	0.667; 1.702	0.789
No	92	76.84	454	73.94			
Seric Albumine < 2.5 mg/dL							
Yes	16	13.44	43	7.21	1.997	1.094; 3.645	***0.024***
No	103	86,55	553	92.78			
Recurrence							
Yes	13	10.92	113	18.95	1.907	1.044; 3.485	***0.035***
No	106	97.47	483	94.79			
Re-infection							
Yes	3	2.52	31	5.20	2.121	0.655; 6.871	0.209
No	116	97.41	565	94.8			
Deaths 0-30 days							
Yes	15	12.60	61	10.23	1.264	0.365;1.005	0.812
No	104	87.39	535	89.76			
Deaths 0-6 months							
Yes	38	31.93	148	21.97	1.665	1.085; 2.555	***0.019***
No	81	68.06	448	78.02			

posed to those with CDI alone, such as younger age, male gender and PPI consumption. The high percentage of cases of community origin suggests the worrying spread of infection in the community, but also the increased susceptibility related to some risk factors for CDI, as immunodepression of patients with chronic hepatopathies, hypoalbuminemia, imbalances of colonic microbiome and low gastric acidity levels, mainly related to the chronic prophylaxis with PPI in cirrhotic patients.

A previous study conducted in the USA (Olsen, 2015) was concordant with our results of correlation the recurrences with the association of CLD. These data, on patients with CDI, should be considered for developping a prognostic score of relapse [32].

No correlation of CLD was found related to CDI with mortality within the first 30 days, with the duration of hospitalization or with the duration until the normalization of the stools. These data suggest that CLD does not significantly influence the severity of the episode of CDI. On the other hand, higher mortality in the first 6 months after the disease, as well as a higher rate of relapses, may indicate the influence of CDI on the bad prognosis of patients with chronic liver disease.

CONCLUSIONS

Preventing CDI in patients with chronic hepatopathies should aim to reduce the susceptibility to the risk factors, by correcting the hypoalbuminemia rebalancing the gut microbiota and limiting the use of PPIs, to well-established criteria. Subsequent studies will evaluate the eficacy of CD screening in healthy carriers before the admition in the hospital departments of hepatology.

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