

# *Clostridium difficile* Infection in Hospitalized Cirrhotic Patients with Hepatic Encephalopathy

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## ABSTRACT

**Background & Aims:** Patients with liver cirrhosis are at-risk population for *Clostridium difficile* infection (CDI). There is a paucity of data on the incidence of CDI in cirrhotics with hepatic encephalopathy (HE). The aim of the study was to evaluate the incidence and risk factors for CDI in cirrhotics hospitalized with HE.

**Methods:** A retrospective analysis of all cirrhotics with HE admitted at a tertiary referral center from January 2012 to December 2014 was made. Patients' medical charts were reviewed, and demographics, laboratory parameters, antibiotics use, etiology of cirrhosis, and therapy of HE, as well as the results of stool samples for toxins A and B (enzyme immunoassay) were carefully searched. The presence of toxin A or B (or both) in stool samples was defined as CDI. Data on cirrhotics with HE and CDI (study group) were compared with those from patients without CDI (control group).

**Results:** A total of 231 cirrhotic patients were hospitalized with HE mostly stage 2 and 3, and 17 (7.3%) of them were diagnosed with CDI. The overall CDI incidence rate was 57.2 cases per 10,000 patient-days. As compared with control patients, those with HE and CDI were more likely to have older age, increased serum creatinine level, hepatorenal syndrome (HRS), and more prior hospitalizations. On multivariate analysis, antibiotic therapy, age over 65 years, and HRS remained significantly related with the development of CDI.

**Conclusion:** Hospitalized cirrhotics with HE are at risk for developing CDI, and clinicians treating such patients should be aware of this infection as rapid detection and prompt treatment may improve outcomes.

**Key words:** risk factors – liver cirrhosis – incidence – *Clostridium difficile* – hepatic encephalopathy.

**Abbreviations:** CDI: *Clostridium difficile* infection; CI: confidence interval; EIA: enzyme immunoassay; HE: hepatic encephalopathy; HRS: hepatorenal syndrome; MELD: Model for End-Stage Liver Disease; OR: odds ratio; PPIs: proton pump inhibitors; SBP: spontaneous bacterial peritonitis.

## INTRODUCTION

Hepatic encephalopathy (HE) is the second most frequent major complication of liver cirrhosis following ascites, characterized by a wide spectrum of neurological or psychiatric symptoms, ranging from minimal disturbances in mental function to deep coma [1-4]. Once it has developed, HE becomes one of the most debilitating disturbances, affecting the lives of both patients and caregivers, with frequent hospitalizations, high 1-year

mortality, and high healthcare costs [5-7]. The pathophysiology of HE is multifactorial, complex and largely unknown, but it is thought to be driven by cerebral edema as a result of the combined action of hyperammonemia, systemic inflammation and oxidative stress [8, 9]. Current therapies for HE are directed at reducing the production and absorption of gut-derived ammonia levels by increasing its removal from the gut [1, 10-12]. The non-absorbable disaccharide lactulose is the mainstay of therapy for a hospitalized cirrhotic patient with HE [1, 13]. Antibiotics are also used; however, they may be associated with serious adverse events such as ototoxicity and nephrotoxicity (neomycin and paromomycin), peripheral neuropathy (metronidazole), and alteration of intestinal microbiota resulting in diarrhea [13, 14]. Rifaximin, a non-absorbable antibiotic, is safer than other antibiotics used in the treatment of HE, and is commonly used in those patients who do not tolerate lactulose. It is recommended by current

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guidelines as an effective add-on therapy to lactulose for prevention of overt HE recurrence [1]; several studies found that rifaximin was equally effective as lactulose for either HE treatment or prevention [15-20].

Over the past two decades there has been a dramatic worldwide increase in both incidence and severity of *Clostridium difficile* infection (CDI) [21, 22]. Paralleling the increased incidence of CDI in the general population, there has been increased interest for CDI in patients with liver disease, particularly in those with liver cirrhosis who are at high risk for CDI development because of their frequent and prolonged hospitalizations, the antibiotic treatment and proton pump inhibitor (PPI) use and the multiple comorbidities [23-27]. In addition, altered immune mechanisms and gut microbiota in cirrhotic patients predispose to various bacterial infections, including CDI [23, 24]. It is therefore somehow surprising that the incidence of CDI in cirrhotics with HE has not been assessed, although such patients have all the above mentioned risk factors for CDI. To our knowledge, there is only one study which evaluated the incidence of CDI in cirrhotic patients treated with rifaximin for HE, reporting the absence of this infection in this set of patients [28]. Thus, our study is the first to assess the incidence of CDI in all hospitalized cirrhotic patients with HE, regardless of the therapy they received.

The aim of this study was to evaluate the incidence and risk factors for CDI in patients with liver cirrhosis hospitalized for an episode of HE in a tertiary-care center.

## PATIENTS AND METHODS

This is a retrospective analysis of patients with liver cirrhosis who were admitted with an episode of HE, from January 1, 2012 to December 31, 2014, at the Institute of Gastroenterology and Hepatology of Iasi, a tertiary referral center for North-East Romania. The patient medical charts were reviewed, and demographic information including age, gender, prior hospitalizations, clinical and laboratory parameters, etiology of cirrhosis, therapy for HE, antibiotics and PPIs use were carefully searched, as well as the presence of the hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), gastrointestinal bleeding, and ascites. All patients developing diarrhea ( $\geq 3$  watery stools/day) were tested for CDI. The results of stool samples for toxins A and B (enzyme immunoassay, EIA) were analyzed, and the presence of any or both toxins was defined as CDI. Each patient's stool was tested only once. Length of hospital stay and mortality during admission were also analyzed. Hepatic encephalopathy was classified according to the West Haven criteria [29].

Cirrhotics with HE and CDI (study group) were compared with those without CDI (control group). As this is a retrospective study, no institutional approval was required.

### Statistical analysis

Statistical analysis was carried out using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution are expressed as mean  $\pm$  SD, otherwise median and the quartiles are used (Q1, Q3). Categorical variables are expressed as absolute values and percentages. Quantitative variables with normal distribution

were compared using the Student's *t* test, while for those with non-normal distribution, the Mann-Whitney test was used. The Chi square test (Fisher exact test for small expected frequencies) was applied for categorical data. Univariate analysis was performed for each recorded variable. Variables with *P*-value  $< 0.1$  in univariate analysis were included in multivariate analysis (logistic regression). Odds ratio (OR) with 95% confidence interval (CI) was calculated for qualitative variables included in the logistic regression. *P* value of less than 0.05 was considered statistically significant.

## RESULTS

Between January 2012 and December 2014, 231 cirrhotic patients with HE were admitted, of whom 17 (7.3%) were diagnosed with CDI. The overall CDI incidence rate was 57.2 cases per 10,000 patient-days. In all the 17 patients, diarrhea occurred later than 72 hours after admission, and therefore, all cases of CDI were considered hospital-acquired. Demographics and clinical and laboratory characteristics of all patients as well as of those with and without CDI are shown in Table I. The majority of patients were male (56.7%), mean age was  $60.9 \pm 10.3$  years, and the most frequent cause of cirrhosis was alcohol consumption (62.4%). Most patients had HE stage 2 (68.4%) or stage 3 (29.4%) and severe liver disease [Model for End-Stage Liver Disease (MELD) median score 15; Child-Pugh score 9.5]. Approximately three quarters of the patients were on PPIs for unspecified reasons.

There was no significant difference in the gender distribution, etiology of cirrhosis, severity of liver disease (MELD score, Child-Pugh score), encephalopathy stage, presence of some complications of cirrhosis (ascites, SBP, upper gastrointestinal bleeding), as well as for most of the laboratory parameters between cirrhotics with HE with CDI and those without CDI (Table I). However, the patients with CDI were significantly older ( $62.8 \pm 10.8$  years vs.  $58.6 \pm 10.1$  years,  $P=0.028$ ), had significantly higher levels of blood creatinine (1.0 mg/dl vs. 0.83 mg/dl;  $P=0.046$ ) and more frequent HRS (52.9% vs. 15.4%;  $P=0.01$ ), but they had a similar number of hospitalizations in the previous three months ( $P=0.779$ ).

During hospitalization, a large proportion of patients with and without CDI received rifaximin as therapy for HE (83.9%), and 50.2% were treated with quinolones or cephalosporines for SBP, urinary or respiratory tract infections, and skin infections. In addition to the patients diagnosed with CDI, 33 (14.2%) developed diarrhea during therapy for HE, but all of them proved negative for *Clostridium difficile* (*C. difficile*) after the stool analysis, and diarrhea resolved with antimotility agents.

The therapy for HE consisted of lactulose (16.3%), rifaximin (21.2%), or a combination of lactulose and rifaximin (62.5%). Metronidazole 500 mg 3 times daily and vancomycin 125 mg 4 times daily were used for treating CDI in 6 (35.3%) and 11 (64.7%) patients, respectively. The mean duration of treatment for CDI was of 10 days.

The results of the univariate and multivariate logistic regression analyses are shown in Table II. Variables with *P*-value  $< 0.1$  in the univariate analysis were included in the multivariate logistic regression: age, antibiotic therapy, SBP, and HRS. Age over 65 years, antibiotic therapy and HRS

**Table I.** Patient demographics, clinical and laboratory parameters of all patients, and according to study groups

| Parameter                                                | All patients<br>n=231      | Study group<br>n=17     | Control group<br>n=214    | P-value            |
|----------------------------------------------------------|----------------------------|-------------------------|---------------------------|--------------------|
| Gender, male/female (%)                                  | 130/101 (56.7/43.3)        | 11/6 (64.7/35.3)        | 119/95(55.6/44.4)         | 0.467 <sup>C</sup> |
| Age, years, mean±SD                                      | 60.9±10.3                  | 62.8±10.8               | 58.6±10.1                 | 0.028 <sup>T</sup> |
| Etiology of cirrhosis, n (%)                             |                            |                         |                           |                    |
| HCV                                                      | 50 (21.6)                  | 4 (23.5)                | 46 (21.5)                 | 0.552 <sup>F</sup> |
| HBV                                                      | 37 (16.0)                  | 4 (23.5)                | 33 (15.4)                 |                    |
| Alcohol                                                  | 144 (62.4)                 | 9 (53.0)                | 135 (63.1)                |                    |
| Child-Pugh class A/B/C, n (%)                            | 16/92/108<br>(7.4/42.6/50) | 0/5/10<br>(0/33.3/66.7) | 16/87/98<br>(8/43.2/48.8) | 0.284 <sup>C</sup> |
| Child-Pugh score, median (Q1/Q3)                         | 9.5(8/12)                  | 11(9/12)                | 9(8/12)                   | 0.151 <sup>M</sup> |
| MELD score, median (Q1/Q3)                               | 15 (11/20)                 | 13.5 (11.25/18.5)       | 15 (11/20)                | 0.901 <sup>M</sup> |
| Prior hospitalization (last 3 months),<br>median (Q1/O3) | 1 (1/3)                    | 1 (1/3.5)               | 1 (1/3)                   | 0.779 <sup>M</sup> |
| Creatinine (mg/dl), median (Q1/Q3)                       | 0.84 (0.64/1.2)            | 1.0 (0.74/2.04)         | 0.83 (0.64/1.2)           | 0.046 <sup>M</sup> |
| Albumin (g/l), median (Q1/Q3)                            | 3 (2.56/3.5)               | 2.5 (2.3/3.4)           | 3 (2.56/3.5)              | 0.063 <sup>M</sup> |
| Bilirubine (mg/dl),<br>median (Q1/Q3)                    | 3 (1.78/5.67)              | 3.42 (1.89/6.84)        | 2.98 (1.78/5.68)          | 0.670 <sup>M</sup> |
| INR, median (Q1/Q3)                                      | 1.5 (1.29/1.75)            | 1.48 (1.23/1.89)        | 1.5 (1.3/1.75)            | 0.960 <sup>M</sup> |
| Ascites, n (%)                                           | 181 (78.4)                 | 15 (88.2)               | 166 (77.6)                | 0.539 <sup>F</sup> |
| SBP, n (%)                                               | 25 (10.8)                  | 4 (23.5)                | 21 (9.8)                  | 0.096 <sup>F</sup> |
| HRS, n (%)                                               | 42 (18.2)                  | 9 (52.9)                | 33 (15.4)                 | 0.01 <sup>F</sup>  |
| UGIB, n (%)                                              | 29 (12.6)                  | 1 (5.9)                 | 28(13.1)                  | 0.703 <sup>F</sup> |
| Encephalopathy, n (%)                                    |                            |                         |                           |                    |
| stage I                                                  | 4 (1.7)                    | 0 (0)                   | 4 (1.9)                   | 0.330 <sup>F</sup> |
| stage II                                                 | 158 (68.4)                 | 9 (52.9)                | 149 (69.6)                |                    |
| stage III                                                | 68 (29.4)                  | 8 (47.1)                | 60 (28.0)                 |                    |
| stage IV                                                 | 1 (0.4)                    | 0 (0)                   | 1 (0.5)                   |                    |
| Antibiotic therapy, n (%)                                |                            |                         |                           |                    |
| Rifaximin                                                | 219 (94.8)                 | 16 (94.1)               | 203 (94.9)                | 0.990 <sup>F</sup> |
| Other antibiotics                                        | 113 (48.9)                 | 14 (82.4)               | 99 (46.3)                 | 0.004 <sup>C</sup> |
| Lactulose, n(%)                                          | 169 (73.2)                 | 9 (52.9)                | 155 (71.4)                | 0.088 <sup>C</sup> |
| PPIs therapy, n (%)                                      | 180 (77.9)                 | 13 (76.5)               | 167 (78.0)                | 0.990 <sup>F</sup> |
| Hospitalization days, median (Q1/Q3)                     | 12 (8/17)                  | 12 (8.5/17)             | 11 (8/12)                 | 0.434 <sup>M</sup> |
| Death during hospitalization, n (%)                      | 36 (15.6)                  | 3 (17.6)                | 33 (15.4)                 | 0.734 <sup>F</sup> |

HBV: chronic hepatitis B virus; HCV: chronic hepatitis C virus; HRS: hepatorenal syndrome; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease; PPIs: proton pump inhibitors; SBP: spontaneous bacterial peritonitis; UGIB: upper gastrointestinal bleeding. C Chi square test; F Fisher exact test; T *t* test (Student); M Mann-Whitney U test.

remained significantly associated with the development of CDI in cirrhotic patients with HE.

## DISCUSSION

Several studies have examined the incidence of CDI in adult hospitalized cirrhotic patients, and most of them reported higher rates of CDI in these patients than in the general population [23-27]. This is not surprising given the high-risk of cirrhotics for bacterial infections [30-32]. The patients with liver cirrhosis have many of the well-known risk factors for CDI: frequent and prolonged hospitalizations, frequent antibiotics and PPIs use, and an immunocompromised system [33]. In addition to the cirrhotic patients, there are other comparable chronically ill subgroups of patients including those with inflammatory bowel disease (ulcerative colitis, Crohn's disease) in whom an increased risk of CDI is well

documented [34]. It was found that cirrhotic patients with CDI had a higher mortality and higher hospital costs, and had a longer length of hospital stay than those without CDI [25]. Moreover, it was shown that CDI yields the highest fatality rate among infections that occur in hospitalized patients with cirrhosis [35]. Given the high incidence of CDI and its negative impact on the outcome of hospitalized cirrhotic patients, a recently published study [36] suggested that all these patients should be screened for CDI; however, the model used in this study did not include the new therapy for CDI, and the results are in contrast with the current guidelines which do not recommend screening of asymptomatic patients.

There is currently a paucity of data on the incidence of CDI in hospitalized cirrhotics with HE, the second most frequent major complication of liver cirrhosis following ascites. To the best of our knowledge, there is only one retrospective study evaluating the incidence of CDI in cirrhotic patients who

**Table II.** Univariate and multivariate regression analysis of risk factors associated with *Clostridium difficile* infection in cirrhotic patients with hepatic encephalopathy

| Parameter                               | Univariate analysis |              |         | Multivariate analysis |              |         |
|-----------------------------------------|---------------------|--------------|---------|-----------------------|--------------|---------|
|                                         | OR                  | 95%CI        | P-value | OR                    | 95%CI        | P-value |
| Age >65 years                           | 4.83                | 1.64-14.25   | 0.002   | 4.029                 | 1.271-12.773 | 0.018   |
| Antibiotic therapy other than rifaximin | 5.42                | 1.51-19.41   | 0.004   | 3.917                 | 1.011-15.174 | 0.048   |
| SBP                                     | 2.82                | 0.845-9.460  | 0.096   | 1.754                 | 0.453-6.784  | 0.416   |
| HRS                                     | 6.17                | 2.220-17.147 | 0.001   | 4.059                 | 1.387-11.879 | 0.011   |
| Prior hospitalizations ( $\geq 2$ )     | 1.033               | 0.384-2.778  | 0.949   | -                     | -            | -       |
| Lactulose                               | 0.731               | 0.463-1.153  | 0.102   | -                     | -            | -       |
| Rifaximin                               | 0.992               | 0.877-1.122  | 0.896   | -                     | -            | -       |
| Creatinine >1.2 mg/dl                   | 1.176               | 0.396-3.486  | 0.778   | -                     | -            | -       |
| UGIB                                    | 0.415               | 0.053-3.254  | 0.703   | -                     | -            | -       |
| PPIs                                    | 0.915               | 0.285-2.937  | 0.990   | -                     | -            | -       |
| Ascites                                 | 2.169               | 0.479-9.817  | 0.539   | -                     | -            | -       |

CI: confidence interval; HRS: hepatorenal syndrome; OR: odds ratio; PPIs: proton pump inhibitors; SBP: spontaneous bacterial peritonitis; UGIB: upper gastrointestinal bleeding.

received rifaximin for the treatment of HE; none of the 211 patients developed CDI during rifaximin therapy [28]. Another study, published as abstract [37], also assessing the efficacy of rifaximin in HE, reported no cases of CDI. Furthermore, a systematic review and meta-analysis reported that rifaximin has a beneficial effect on HE and none of the included trials found an increased risk of CDI [19]. It was suggested that CDI is absent or it occurs very rarely in cirrhotics with HE, probably due to the protective effect of lactulose (by reducing short chain fatty acids production and suppressing *C. difficile* growth) [23] and rifaximin (by reducing enteric ammonia-producing bacterial loads) [13].

The present study investigates the incidence of CDI in all hospitalized cirrhotic patients with HE, regardless of the therapy they received. We found that 7.3% of cirrhotics admitted for an episode of HE developed CDI. This finding contradicts the results of the two studies mentioned above [28, 37], which reported the absence of CDI in patients treated with rifaximin for HE. The high incidence of CDI in our study could, at least partially, be explained by the systematic stool testing for toxins A and B by EIA in all cirrhotic patients hospitalized with HE who developed diarrhea during therapy. In addition, all our patients with HE diagnosed with CDI had several additional risk factors for CDI, including the use of antibiotics, advanced age, and an immune compromised system secondary to liver cirrhosis [28]. Rifaximin, unlike the other antibiotics used for the treatment of HE, appears to be effective, safe and well tolerated [16, 17, 28, 38]. Other studies suggested rifaximin to be effective in the prevention and treatment of the recurrent CDI [39, 40]. We should also mention that, in Romania, rifaximin is often used alone or in combination with lactulose in the treatment of HE. Although most studies regarding the long-term therapy with rifaximin show that the risk for CDI is absent or negligible, it should, however, be underlined that such a risk does exist, as demonstrated by our study, and some other cases reported in literature [16, 17]. Bass et al. [16] in a randomized, double-blind, placebo-controlled trial,

demonstrated that rifaximin significantly reduced the risk for an episode of HE as compared to a placebo over a 6-month period, and reported that 2 out of 140 patients (1%) who had received rifaximin developed CDI during treatment (none of the placebo group), but both patients presented several risk factors for CDI. A number of other cases of CDI, detected in long-term rifaximin therapy, were also reported [41, 42]. Mullen et al. [41] found 6 cases of CDI (0.015%) in a cohort study of patients who had received rifaximin for at least 24 months; infections occurred in high-risk patients. These rare cases of CDI reported during rifaximin therapy indicate that there is a risk for this infection, and the prescription of a long-term treatment with this antibiotic requires “a note of caution” [43].

Diarrhea in cirrhotic patients with HE may represent an adverse effect of the therapy used for HE, mostly of lactulose [11, 14] and very rarely of rifaximin [44]. According to the study by Neff et al. [28], 8% of their patients developed diarrhea during treatment with rifaximin, while none was diagnosed with CDI. Another study reported that less than 5% of the patients developed diarrhea while receiving rifaximin for the treatment of HE [44].

Our study has some strengths and also has several limitations. Thus, it is the first study evaluating the incidence using internationally recognized CDI surveillance definitions [45], and the risk factors of CDI among hospitalized cirrhotics with HE at a Romanian tertiary referral center. However, as a retrospective, single center study it is more likely to produce bias: undertesting for *C. difficile*, underdiagnosed CDI in some cases, missing data. In addition, the study provides no information on the *C. difficile* strain.

## CONCLUSION

The hospitalized cirrhotic patients with HE are at risk for CDI during therapy with lactulose/rifaximin. Clinicians should have a high index of suspicion for CDI when evaluating

cirrhotic patients hospitalized with HE who develop diarrhea, in order to rapidly diagnose and treat this infection. Further studies on CDI incidence and impact in patients with liver cirrhosis hospitalized for HE are warranted.

**Conflicts of interest:** No conflict to declare.

**Authors' contribution:** O.C.S. and I.G.: patients' enrollment, data collection, analysis and interpretation; C.S.: concept and design of the study, manuscript drafting and writing, critical revision of the final version; C.C. and E.M.: data acquisition and interpretation, manuscript writing; L.B.: statistical analysis, manuscript editing; A.T.: study planning and design, editing and critical revision of the manuscript for important intellectual content. All authors approved the final version for publication.

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