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Clostridioides difficile Infection in Patients with Cirrhosis Treated for Hepatic Encephalopathy

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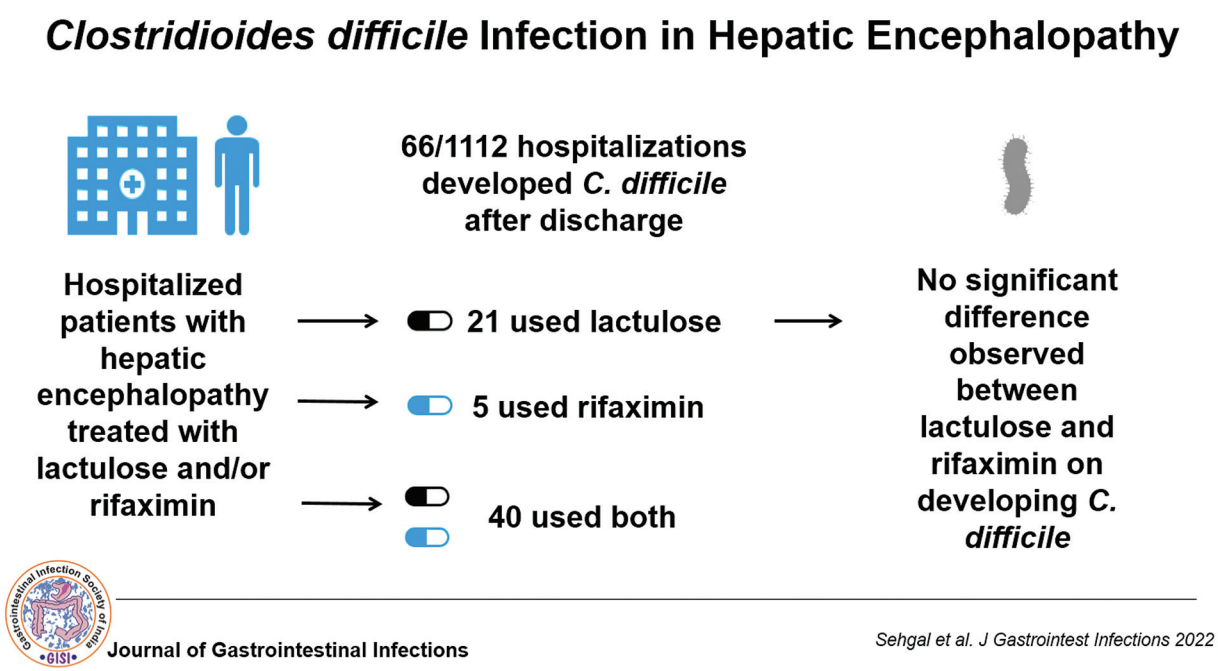

Graphical representation of study flow methodology and results.

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Abstract

Introduction Hospitalizations, proton-pump inhibitors (PPI), and systemic antibiotics increase the risk of *Clostridioides difficile* infection (CDI) in cirrhosis. We compare the risk of CDI with hepatic encephalopathy (HE) medications, hypothesizing that rifaximin may decrease CDI risk.

Materials and Methods A retrospective study of hospitalized HE patients treated with lactulose and/or rifaximin at Mayo Clinic Minnesota, Florida, and Arizona from 2008 to 2013 was conducted. Data on demographics, hospitalizations, antibiotics, and PPI use and CDI were gathered. Univariate and multivariable cox models were constructed.

Results We found 1,112 hospitalizations in 1,055 unique patients (55 had 1 subsequent readmission, 1 patient had 2); 428 (40.6%) patients were women (median age: 58 years [interquartile range: 52–65]). CDI developed after 66/1,112 (5.9%) hospitalizations within 12 months post-discharge. Lactulose was administered in 21 (31.8%), rifaximin in 5 (7.6%), both in 40 (60.6%) hospitalizations. Systemic antibiotics were used in 28 (42.4%) patients and PPIs in 60 (90.9%) patients.

Univariate analysis using medication (with lactulose alone as the reference group) showed rifaximin was not significantly associated with CDI compared with lactulose (hazard ratio [HR]: 1.57, 95% confidence interval [CI]: 0.57–4.33, $p = 0.39$). Use of both medications was not significant compared with lactulose (HR: 1.41, 95% CI: 0.84–2.38, $p = 0.19$). Results were similar after controlling for confounders. Multivariable analysis based on length of stay, age, and gender showed no differences between rifaximin versus lactulose and both versus lactulose.

Conclusion There is no significant difference between lactulose and rifaximin on CDI development in HE patients. However, CDI should still be considered when managing diarrhea in HE patients.

Keywords

- cirrhosis
- *Clostridioides difficile*
- hepatic encephalopathy
- lactulose
- rifaximin

Introduction

Clostridioides difficile infection (CDI) is the most common cause of infectious diarrhea in hospitalized patients. The incidence of both primary and recurrent CDI is increasing and incurs high health care costs.[1] Patients with cirrhosis are at an increased risk of developing CDI due to frequent hospital admissions for the treatment of complications of cirrhosis, exposing them to an environment in which they are more likely to contract CDI. Additionally, the presence of comorbidities, suppressed immune system, and the use of antibiotics and proton-pump inhibitors (PPIs) are common in patients with cirrhosis and are known risk factors for the development of CDI.[2]

C. difficile is also associated with poor outcomes in hospitalized patients with cirrhosis.[3] Patients with cirrhosis are often hospitalized with hepatic encephalopathy (HE) as a complication of the disease. Treatment of HE includes the administration of lactulose and/or the antibiotic rifaximin. Studies suggest that rifaximin, a nonsystemic gut-selective antibiotic, has been demonstrated to have bactericidal activity against *C. difficile,*[4] and therefore, its use in patients with cirrhosis may decrease the risk of developing CDI.[5] Lactulose is known to exert beneficial prebiotic effects in the human gut microbial environment, perhaps protecting from dysbiosis, possibly decreasing the risk of acquiring CDI.[6]

Studies also have shown a potential decrease in the risk of CDI development with lactulose or rifaximin treatment but have not compared the two treatments.[7,8] This study compares the effect of lactulose and rifaximin treatment on the risk of CDI development, hypothesizing that rifaximin may decrease the risk of CDI compared with lactulose.

Materials and Methods

This was a multicenter retrospective study of all hospitalized cirrhotic patients treated for HE with lactulose, rifaximin or both at Mayo Clinic Minnesota, Florida and Arizona from January 1, 2008 to December 31, 2013. This was a study utilizing a historical cohort. Hospitalized patients treated with lactulose and/or rifaximin were identified using the pharmacy database. Data collected included demographics, pharmacy medication administration records, admission, discharge, previous hospitalizations, laboratory results, antibiotic and PPI use, and dates of CDI episodes. A diagnosis of CDI was made by a positive polymerase chain reaction test. Episodes of CDI occurring post-discharge were accounted for, while prior infections (those occurring before the discharge) were considered as a risk factor for acquiring CDI. The study outcome period was the first 12 months following discharge.

Statistical Analysis

Cox models were constructed using time-dependent intervals to account for varying lengths of follow-up and changes in medication use over time. After a CDI event was observed, subjects were no longer considered at risk for a new infection

Table 1 Comparison of baseline characteristics between patients who did not develop *Clostridium difficile* infection and patients who did (CDI—*C. difficile* infection, IQR—interquartile range)

Characteristics	Patients who did not develop CDI ($n = 991$)	Patients who developed CDI ($n = 64$)	*p*-Value
Age	58 years (IQR: 52–65)	59 years (IQR: 54–65)	0.87
Gender (women)	399 (40.3%)	29 (45.3%)	0.43
Length of Stay	5 days (IQR: 3–9)	6 days (IQR: 3–16.5)	0.11
Antibiotic use	385 (38.8%)	27 (42.2%)	0.64
Proton pump inhibitor use	836 (84.4%)	58 (90.6%)	0.17
Treatment			0.36
Lactulose only	389 (39.3%)	20 (31.2%)	
Rifaximin only	71 (7.2%)	5 (7.8%)	
Both medications	531 (53.6%)	39 (60.9%)	

for 6 months. Infections occurring within 6 months from the first episode were considered as a recurrence, while those occurring after 6 months were considered a new infection. Time periods outside of 1-year post-hospitalization were not included in the analysis. Hazard ratio (HR) and corresponding 95% confidence intervals (CI) were used to provide estimates of effect. This study was approved by the ethics committee.

Results

A total of 1,112 hospitalizations in 1,055 unique patients (55 had 1 subsequent readmission and 1 patient had 2) were found (►**Table 1**). The median MELD score was 16.63 (interquartile range: 10.55–22.88). *C. difficile* infection developed in 66 (5.9%) hospitalizations (65 unique patients) within 12 months post-discharge (►**Table 1**). Of these, lactulose was administered in 21 (31.8%) hospitalizations, rifaximin in 5 (7.6%) and both in 40 (60.6%) hospitalizations. Systemic antibiotics were used in 28 (42.4%) admissions and PPIs in 60 (90.9%) admissions.

Univariate analysis based only on medication administered (using lactulose alone as the reference group), regardless of dosage, showed that rifaximin alone was not significantly associated with CDI development as compared with lactulose alone (HR: 1.57, 95% CI: 0.57–4.33, $p = 0.39$). Use of both medications was also not significant when compared with lactulose alone (HR: 1.41, 95% CI: 0.84–2.38, $p = 0.19$). The results were similar after controlling for confounders with multivariable analysis, including length of stay, age, and gender.

Discussion

In our cohort, CDI developed in a small number of patients with cirrhosis within 12 months follow-up post-discharge. Our study revealed no significant difference between lactulose and rifaximin and the risk of developing CDI in patients with HE.

Food and Drug Administration approval for rifaximin use is for the prevention of HE recurrence, but it is commonly used for treatment.[9] Prior studies have shown a very low risk of CDI with chronic rifaximin use in patients with cirrhosis.[7] One such study was performed in 299 patients who were in remission from HE and were randomized to receive either rifaximin (140 patients) or placebo (159 patients).[10] This study showed that less than 2% (2/140) of patients treated with rifaximin developed CDI as compared with none in the placebo group. Another study of cirrhotic patients on rifaximin revealed that almost one-third of those who developed diarrhea were positive for CDI.[11] Lactulose alters the gut microbial environment in ways that can inhibit *C. difficile* growth.[12] A nested case–control study of hospitalized patients with end-stage liver disease was conducted to determine the association of lactulose use with developing CDI.[8] Cases were patients with incident diagnosis of CDI during admission. They evaluated the use of lactulose for more than 48 hours and exhibited that lactulose use was associated with a significantly lower risk of CDI as compared with matched controls (matched for age, sex, admission date, and length of hospital stay).[8] Our study supports these findings of lower rates of infection in patient receiving lactulose or rifaximin treatment for HE.

Therapy for HE is based on the disease severity, with higher grade HE often treated with a combination of rifaximin and lactulose.[9,13] Patients with more severe disease often have a prolonged stay in the hospital and receive antibiotics for their treatment, which puts them at an increased risk of CDI.[14]

Our results must be interpreted with caution as treatment was not randomized amongst patients. Being a retrospective study, it was also not possible to account for drivers of treatment choice in patients. Rifaximin alone was only administered to five patients, making it a small group to draw significant comparisons from. Also, the duration for which lactulose and rifaximin was administered in these patients is not available. Further, since data in our study dates back to 2013, our cohort is historic.

In conclusion, patients with cirrhosis complicated by HE are exposed to several risk factors that can predispose them to develop CDI. In our study, this risk did not appear to depend on whether rifaximin and/or lactulose are used for the management of HE; however, further research is needed to establish the risk difference between the different treatment groups of HE.

Our study revealed that there is no difference between lactulose and rifaximin on CDI development in HE patients. While both medications might be safe, CDI should still be considered when managing HE patients who develop diarrhea.

Note

These data were presented as a poster at American College of Gastroenterology 2021.

Ethics Approval

This study was approved by the ethic committee.

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Conflict of Interest

None declared.

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