# Rifaximin Improves the Treatment of Hepatic Encephalopathy

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## Study Overview

Objective. To determine whether rifaximin, an antibiotic with minimal absorption, improves the prevention of acute hepatic encephalopathy.

Design. Double-blind, placebo-controlled randomized trial with rifaximin administered in a dose of 550 mg twice daily to the intervention group. Seventy sites for enrollment were present in the United States, Canada, and Russia, and the trial was designed to last 6 months.

Setting and participants. 299 patients with chronic liver disease who had prior episodes of hepatic encephalopathy. The sample comprised adults > 18 years with severe cirrhosis who had at least 2 episodes of hepatic encephalopathy over the prior 6 months. Exclusion criteria included expectation of liver transplantation within 1 month after the screening visit, presence of conditions known to increase the risk of hepatic encephalopathy (GI hemorrhage, placement of a portosystemic shunt) within 3 months of the screening visit, chronic renal insufficiency, respiratory insufficiency, anemia, electrolyte abnormalities, or active infection. Subjects were censored upon being lost to follow-up or the development of hepatic encephalopathy. Authors used intention-to-treat analyses conducted through Cox proportional hazard models.

Main outcome measures. The primary endpoint was time to first episode of hepatic encephalopathy (defined as an increase in the Conn score, a standardized scale used to categorize encephalopathy, and/or the development of asterixis). The secondary endpoint was time to first hospitalization for hepatic encephalopathy.

Main results. The mean follow-up was 130 days (standard deviation [SD], 56.5) in the rifaximin group and 105.7 days (SD, 62.7) in the placebo group. Subjects took more than 80% of pills. The mean age was 55.5 years in the rifaximin group (140 patients) and 56.8 years in the placebo group (159 patients). Most patients were male (53.6% and 67.3%) and white (84.3% and 87.4%). 69% of both groups had 2 encephalopathic episodes in the prior 6 months, and the average time since the last episode was over 2 months. More than 90% of patients received concomitant lactulose therapy. Use of additional medications for the treatment of cirrhosis was common with more than one-half of both groups using spironolactone and furosemide; approximately one-third used propranolol or nadolol for the prevention of bleeding esophageal varices. Treatment with rifaximin significantly reduced the risk of hepatic encephalopathy (hazard ratio [HR], 0.42 [95% confidence interval {CI}, 0.28–0.64]; $P < 0.001$). 22.3% of those in the treatment arm had an episode of hepatic encephalopathy compared to 45.9% in the placebo arm. The number needed to treat [NNT] to prevent 1 episode was 4. The significant benefits for rifaximin were evident for most subgroups (defined by gender, race, age, severity of disease, diagnosis of diabetes, duration of remission, prior number of encephalopathic episodes, and prior portosystemic shunt). No significant improvements were evident for subjects not taking lactulose at baseline, those with the most severe disease, and those in the "other" racial category. Rifaximin also decreased the risk of hospitalization from hepatic encephalopathy (HR, 0.50 [95% CI, 0.29–0.87]; $P = 0.01$) with 13.6% hospitalized compared to 22.6% in the placebo arm. The NNT to prevent one hospitalization for hepatic encephalopathy was 9. No difference in adverse effects was evident between the 2 arms; however, 2 cases of *Clostridium difficile* infection occurred in the rifaximin group with zero cases in the placebo arm.

Conclusion. Rifamixin decreases the risk of hepatic encephalopathy.

## Commentary

Hepatic encephalopathy has profound effects on patients with cirrhosis, leading to frequent life disruptions, poor quality of life, and extensive use of health care resources [1]. The development of hepatic encephalopathy also is an independent risk factor for death [2]. Increased systemic level of neurotoxins such as ammonia are thought to be the cause of hepatic encephalopathy, and the most commonly used therapies for treatment and prevention are nonabsorbable disaccharides, such as lactulose [3,4]. Lactulose decreases ammonia absorption through the GI tract by altering colonic pH and by promoting catharsis of gut contents [5]. However, the frequent diarrhea that results from its use, which is required for effectiveness, is often not well tolerated, leading to poor compliance [6].

Antibiotics can be effective in the treatment or prevention of hepatic encephalopathy because they reduce the quantity

of ammonia-producing bacteria in the GI tract. Rifaximin is a minimally absorbed antibiotic with wide coverage of gram-positive and gram-negative bacteria. It has limited side effects and induces little bacterial resistance, leading to its identification as a better candidate for long-term use than other antibiotics [7]. Rifaximin has been tested extensively as a treatment for acute hepatic encephalopathy but is not yet approved for use in the prevention of encephalopathy [8].

This study was a phase 3 study to test the efficacy of rifaximin as a long-term therapy to prevent hepatic encephalopathy. In this trial, administration of rifaximin reduced the development of hepatic encephalopathy by 58% (absolute risk reduction of 23.8%) and reduced hospitalizations from encephalopathy by 50% (absolute risk reduction of 9%). The NNT to prevent 1 hospitalization for hepatic encephalopathy was 9, a result that would easily meet any cost-effectiveness standard. Its potential for quality of life improvements is even more substantial. These findings are important and could fundamentally alter the arsenal of treatments to improve the lives of patients with cirrhosis and recurrent hepatic encephalopathy.

Adverse effects were quite common in both arms of the study, with many symptoms perhaps not attributable to the treatment, such as nausea, diarrhea, and fatigue. The one major concern with chronic administration of an antibiotic like rifaximin, even with its minimal absorption, is infection. Infections were similar in both arms, but 2 subjects developed *C. difficile* infections on rifaximin compared with no subjects in the placebo arm. Both subjects did well with treatment of *C. difficile*, and the rifaximin was continued through the course of treatment. However, *C. difficile* can be a severe infection with devastating consequences, and the incidence of infection with rifaximin should be followed closely to determine how important the complication is with widespread use of rifaximin.

This study had a few limitations or concerns. First, despite being adequately powered to detect clinically meaningful differences, the sample size was small. Second, the sample had limited racial diversity, limiting the subgroup analysis by race to only 2 categories—white and other. Third, the manufacturers of rifaximin financed the study. Most of the authors had very close financial relationships with the manufacturer, and a consultant hired by the company contributed to the writing of the manuscript.

Further research must be done to further explore the effects of rifaximin for the prevention of hepatic encephalopathy. The incidence of *C. difficile* infection should be followed closely. The dose of lactulose required for effective prevention, when used in combination with rifaximin, should be examined to determine if the dose of lactulose could be decreased if used in combination or discontinued altogether. This study provided no direct information about this, and the results among patients using rifaximin without lactulose were not significant with a large confidence interval.

## Applications for Clinical Practice

Use of rifaximin for the prevention of hepatic encephalopathy among patients with cirrhosis is effective. Because of the devastating effects of recurrent hepatic encephalopathy, rifaximin should be considered for routine use, especially among patients with cirrhosis who have recurrent encephalopathy.

*—Review by Jason P. Block, MD, MPH*

## References


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