EDITORIALS

# Gut Flora and Hepatic Encephalopathy in Patients with Cirrhosis

Stephen M. Riordan, M.D., and Roger Williams, M.D.

Hepatic encephalopathy that is a complication of cirrhosis is not a uniform clinical entity; rather, it encompasses a spectrum of neuropsychiatric disturbances affecting motor function, cognition, personality, and consciousness.[1] Clinical manifestations range from coma to subtle cognitive abnormalities detectable only on psychometric or neurophysiologic testing. The mild manifestation of hepatic encephalopathy, termed minimal hepatic encephalopathy, is estimated to affect up to 60% of patients with cirrhosis[2] and may seriously impair a patient's daily functioning and quality of life. Psychomotor slowing and deficits in attention, visual perception, and visuoconstructive abilities are key features, whereas fine motor performance is also impaired. Minimal hepatic encephalopathy can render a patient unfit to drive a motor vehicle and is an important predictor of the development of overt hepatic encephalopathy.[2] Hepatic encephalopathy occurs in approximately 30 to 45% of patients with cirrhosis[3] and portends a poor prognosis. Indeed, the probability of transplant-free survival after the first episode of acute hepatic encephalopathy is only 42% at 1 year and 23% at 3 years.[4]

The pathogenesis of hepatic encephalopathy remains incompletely elucidated, although a central theme of all current hypotheses is that the accumulation of ammonia, predominantly derived from the intestine, plays a crucial role.[1,5] Gut flora, especially urease-containing species, such as klebsiella and proteus species, are an important source of ammonia in humans. The deamination of glutamine in small-intestinal mucosa and, to a lesser extent, renal and muscle synthesis also contribute.[5] In patients with cirrhosis, the accumulation of ammonia results mainly from impaired hepatic clearance due to hepatocellular failure or portosystemic shunting.[1,5] Other gut-derived toxins, such as benzodiazepine-like substances, short- and medium-chain fatty acids, phenols, mercaptans, and manganese, may interact with ammonia to exacerbate neurochemical changes.[1] In addition, a synergistic effect of inflammation is likely to be important in causing hepatic encephalopathy.[6]

The use of nonabsorbed disaccharides or antibiotics (alone or in combination) to reduce the colony counts of ammonia-producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen forms the mainstay of current guidelines for the management of hepatic encephalopathy that is a complication of cirrhosis. This treatment approach is currently suggested for use while a precipitating event, such as sepsis, gastrointestinal bleeding, renal dysfunction, electrolyte imbalance, or constipation, is being reversed and also when no reversible factor is identified.[5]

Despite the widespread, long-standing clinical impression that such therapy is effective, a critical appraisal of relevant trials published from 1969 to March 2003 concluded that the results of those studies did not meet current standards of evidence-based medicine.[7] This analysis has highlighted the need for better-designed studies that can properly assess the efficacy of traditional therapies. However, such studies are particularly difficult to perform, in view of the confounding factors that must be considered and the necessity to enroll adequate numbers of patients with well-defined disease across the clinical spec-

trum of hepatic encephalopathy. Further, standardized definitions, assessment tools, and outcome measures are important for obtaining clinically meaningful results.

Two recent studies have now addressed the efficacy of the nonabsorbed disaccharide lactulose,[2] or the minimally absorbed antibiotic rifaximin used concomitantly with lactulose,[8] for the prevention of recurrent episodes of overt hepatic encephalopathy (rather than to treat an acute episode). The study of rifaximin (ClinicalTrials.gov number, NCT00298038) is described by Bass and colleagues in this issue of the *Journal*.[8] The study of lactulose alone, by Sharma and colleagues, was a single-center study in which 125 patients with cirrhosis who had recovered from at least one previous episode of overt hepatic encephalopathy were randomly assigned to receive lactulose (20 to 40 g daily) or placebo.[2] The two groups were well matched with regard to a range of demographic and clinical baseline characteristics, including the severity of liver disease, presence of large portosystemic shunts, number and severity of previous episodes of overt hepatic encephalopathy, and presence of any precipitating factors. During a median follow-up period of 14 months, significantly fewer patients in the lactulose group than in the placebo group had a recurrent episode of overt hepatic encephalopathy (12 of 61 patients [19.6%] vs. 30 of 64 patients [46.8%], $P=0.001$).

The study by Bass and colleagues was a multicenter, randomized, double-blind, placebo-controlled trial of the efficacy of rifaximin for the prevention of recurrent episodes of overt hepatic encephalopathy in patients with cirrhosis; concomitant lactulose use was permitted during the study period. A total of 299 patients were randomly assigned to receive rifaximin at a dose of 550 mg twice daily (140 patients) or placebo (159 patients) for 6 months. Over 90% of the patients in each group also received lactulose throughout the study period (mean daily dose, 31.4 g in the rifaximin group and 35.1 g in the placebo group). The two groups did not differ significantly with regard to the severity of liver disease or the number of previous episodes of overt hepatic encephalopathy. Over the 6-month study period, the incidence of recurrent, overt hepatic encephalopathy was significantly reduced in the rifaximin group as compared with the placebo group (31 of 140 patients [22.1%] vs. 73 of 159 [45.9%], $P<0.001$). Furthermore, the need for hepatic encephalopathy–related hospitalization was also significantly reduced in the rifaximin group.

Neither the study by Bass and colleagues nor the study by Sharma et al. addresses the effect of lactulose or combined lactulose–rifaximin therapy on gut flora and ammonia production, in particular how changes in the flora and production correlate with the clinical efficacy of the therapy. Nonetheless, the trials add weight to the concept that treatments directed toward modulating gut flora are of value for the management of overt hepatic encephalopathy in patients with cirrhosis, at least for the prevention of recurrent episodes. Substantial rates of treatment failure remain, highlighting the need for additional treatment strategies for this debilitating and potentially life-threatening condition. Further, carefully designed studies are needed to elucidate the role of other approaches to changing the composition of gut flora that currently show promise for the treatment of hepatic encephalopathy, such as the use of probiotics or of prebiotics combined with probiotics.[9,10] Whether it is of benefit to combine therapies that alter the composition of gut flora with measures designed to both increase the tissue detoxification of ammonia[1] and reduce proinflammatory cytokines[6] remains a question. Like assessments of nonabsorbed disaccharides and antibiotics, studies of possible therapies for hepatic encephalopathy should consider potentially confounding pathogenetic factors and should be carried out in a range of well-defined clinical contexts, if the true value of these interventions is to be evaluated properly.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Gastrointestinal and Liver Unit, Prince of Wales Hospital and University of New South Wales, Sydney (S.M.R.); and the Institute of Hepatology, University College London Medical School, and University College London Hospitals, London (R.W.).

1. Riordan SM, Williams R. Treatment of hepatic encephalopathy. N Engl J Med 1997;337:473-9.
2. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137:885-91.
3. Poordad FF. The burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007;25:Suppl 1:3-9.
4. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30:890-5.
5. Blei AT, Cordoba J, Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. Am J Gastroenterol 2001;96:1968-76.

6. Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 2004; 40:247-54.
7. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046-51.
8. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071-81.
9. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with liver cirrhosis. Hepatology 2004;39:1441-9.
10. Malaguarnera M, Gargante MP, Malaguarnera G, et al. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. Eur J Gastroenterol Hepatol 2010;22:199-206.


# Genetic Susceptibility to Hepatic Steatosis

Anna Mae Diehl, M.D.

Noninvasive imaging techniques that quantify tissue triglyceride content, such as proton nuclear magnetic resonance spectroscopy, have shown that the accumulation of triglycerides in the liver (i.e., steatosis) is a highly prevalent condition, occurring in up to one third of adults in the United States.[1] Steatosis is associated with increased mortality from cardiovascular disease, cancer, and liver disease, even after adjustment for other potentially confounding coexisting disorders such as obesity and type 2 diabetes mellitus.[2] Therefore, it is important to understand the processes that regulate hepatic triglyceride content.

The major risk factor for hepatic steatosis is excessive consumption of food, alcohol, or both. However, many people who overconsume do not have fatty livers, yet steatosis can develop in those who do not engage in these behaviors.[3] Thus, genetic or environmental factors, or both, influence one's susceptibility to hepatic triglyceride accumulation.

In this issue of the *Journal*, Petersen et al. present novel evidence that single-nucleotide polymorphisms (SNPs) in the apolipoprotein C3 gene (*APOC3*) are important in this regard.[4] They examined two *APOC3* SNPs in a cohort of Asian Indian men who did not have the typical risk factors for hepatic steatosis, such as excessive alcohol consumption, obesity, overt insulin resistance, or type 2 diabetes. The investigators found a relationship between hepatic triglyceride accumulation and variant alleles at each SNP that increase apolipoprotein C3 expression (so-called high-expression alleles). Proton nuclear magnetic resonance studies detected hepatic steatosis in 38% of subjects with one or more of the variant alleles but in none of those without these alleles. A similar association between the high-expression alleles and hepatic steatosis was found in a cohort of non–Asian Indian men who also did not have the typical risk factors for steatosis. In that cohort, the prevalence of hepatic triglyceride accumulation was 9% among subjects with variant alleles as compared with zero in those without variant alleles. These findings provide compelling evidence linking the increased expression of apolipoprotein C3 with hepatic triglyceride accumulation, while confirming that racial or ethnic factors also influence susceptibility to steatosis.[1]

Petersen et al. also investigated mechanisms that might mediate apolipoprotein C3–related hepatic steatosis. The subjects with high-expression alleles had increased levels of fasting serum triglycerides, increased postprandial levels of circulating triglyceride-rich chylomicrons, and a decreased ability to clear triglyceride from plasma after an intravenous triglyceride challenge. Thus, the investigators concluded that increased levels of apolipoprotein C3 impair the clearance of diet-derived triglyceride-rich particles, resulting in increased hepatic delivery of triglycerides, which in turn leads to hepatic steatosis. This possibility is supported by independent evidence that apolipoprotein C3 inhibits the activity of an enzyme that mediates triglyceride uptake into adipose depots.[5]

One of the most common conditions that alter the storage of triglycerides in adipocytes is insulin resistance.[6] In the study by Petersen et al., glucose-tolerance testing revealed that among the subjects with high-expression alleles, insulin resistance was greater in the subjects with hepatic steatosis than in those without steatosis. The cross-sectional nature of the study confounds efforts to determine whether underlying insulin resistance predisposed the subjects with high-expression *APOC3* alleles to the development of hepatic steatosis. The authors propose an alternative theory based on evidence that weight loss

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# Rifaximin Treatment in Hepatic Encephalopathy

Nathan M. Bass, M.B., Ch.B., Ph.D., Kevin D. Mullen, M.D., Arun Sanyal, M.D., Fred Poordad, M.D., Guy Neff, M.D., Carroll B. Leevy, M.D.,* Samuel Sigal, M.D., Muhammad Y. Sheikh, M.D., Kimberly Beavers, M.D., Todd Frederick, M.D., Lewis Teperman, M.D., Donald Hillebrand, M.D., Shirley Huang, M.S., Kunal Merchant, Ph.D., Audrey Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D.

## ABSTRACT

### BACKGROUND

Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis. The efficacy of rifaximin, a minimally absorbed antibiotic, is well documented in the treatment of acute hepatic encephalopathy, but its efficacy for prevention of the disease has not been established.

### METHODS

In this randomized, double-blind, placebo-controlled trial, we randomly assigned 299 patients who were in remission from recurrent hepatic encephalopathy resulting from chronic liver disease to receive either rifaximin, at a dose of 550 mg twice daily (140 patients), or placebo (159 patients) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy. The key secondary end point was the time to the first hospitalization involving hepatic encephalopathy.

### RESULTS

Rifaximin significantly reduced the risk of an episode of hepatic encephalopathy, as compared with placebo, over a 6-month period (hazard ratio with rifaximin, 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001). A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group, for a hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P=0.01). More than 90% of patients received concomitant lactulose therapy. The incidence of adverse events reported during the study was similar in the two groups, as was the incidence of serious adverse events.

### CONCLUSIONS

Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy. (ClinicalTrials.gov number, NCT00298038.)

From the University of California, San Francisco (N.M.B.), and California Pacific Medical Center (T.F.) — both in San Francisco; Cedars–Sinai Medical Center, Los Angeles (F.P.); University of California, San Francisco, Fresno (M.Y.S.); and Scripps Clinical Research Center, La Jolla (D.H.) — all in California; Metrohealth Medical Center, Case Western Reserve University, Cleveland (K.D.M.), and University of Cincinnati Medical Center, Cincinnati (G.N.) — both in Ohio; Virginia Commonwealth University, Richmond (A.S.); University of Medicine and Dentistry of New Jersey, Newark (C.B.L.); Weill Medical College of Cornell University (S.S.) and New York University School of Medicine (L.T.) — both in New York; Asheville Gastroenterology Associates, Asheville, NC (K.B.); and Salix Pharmaceuticals, Morrisville, NC (S.H., K.M., A.S., E.B., W.P.F.). Address reprint requests to Dr. Forbes at Salix Pharmaceuticals, 1700 Perimeter Park Dr., Morrisville, NC 27560.

*Deceased.

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Approximately 5.5 million persons in the United States have hepatic cirrhosis, a major cause of complications and death.[1-3] Hepatic encephalopathy, a complication of hepatic cirrhosis, imposes a formidable burden on patients, their families, and the health care system.[1,4] Overt episodes of hepatic encephalopathy are debilitating, can occur without warning, render the patient incapable of self-care, and frequently result in hospitalization.[1,4] In 2003, more than 40,000 patients were hospitalized with hepatic encephalopathy, a number that increased to over 50,000 in 2004.[4] Although the occurrence of episodes of hepatic encephalopathy appears to be unrelated to the cause of cirrhosis,[5] increases in the frequency and severity of such episodes predict an increased risk of death.[6,7]

Hepatic encephalopathy is a neuropsychiatric syndrome for which symptoms, manifested on a continuum, are deterioration in mental status, with psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and — in severe forms — coma.[1,7,8] The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by the Conn score (also called West Haven criteria) (on a scale from 0 to 4, with higher scores indicating more severe impairment),[9] and impaired neuromotor function.[1,10] The Conn score is recommended by the Working Party on Hepatic Encephalopathy[8] for assessment of overt hepatic encephalopathy in clinical trials. Signs of neuromotor impairment include hyperreflexia, rigidity, myoclonus, and asterixis (a coarse, myoclonic, "flapping" muscle tremor), which is measured with the use of an asterixis severity scale.[10-12]

Most therapies for hepatic encephalopathy focus on treating episodes as they occur and are directed at reducing the nitrogenous load in the gut, an approach that is consistent with the hypothesis that this disorder results from the systemic accumulation of gut-derived neurotoxins, especially ammonia, in patients with impaired liver function and portosystemic shunting.[2,3,13] The current standard of care for patients with hepatic encephalopathy, treatment with nonabsorbable disaccharides lactitol or lactulose, decreases the absorption of ammonia through cathartic effects and by altering colonic pH.[14]

In an open-label, single-site study, Sharma et al. reported that lactulose, as compared with placebo, was effective in the prevention of overt hepatic encephalopathy.[15] In that study, 125 patients who had recovered from a recent episode of hepatic encephalopathy were randomly assigned, in a 1:1 ratio, to receive either lactulose or placebo for up to 20 months. During a median study period of 14 months, the proportion of patients with episodes was smaller in the lactulose group than in the placebo group (19.6% vs. 46.8%, $P=0.001$). However, side effects of lactulose therapy — including an excessively sweet taste and gastrointestinal side effects such as bloating, flatulence, and severe and unpredictable diarrhea possibly leading to dehydration — result in frequent noncompliance.[16-18]

In general, the oral antibiotics neomycin, paromomycin, vancomycin, and metronidazole have been effectively used, with or without lactulose, to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy.[14,16,17] However, some oral antibiotics are not recommended for long-term use because of nephrotoxicity, ototoxicity, and peripheral neuropathy[19,20] and are specifically contraindicated in patients with liver disease.[19,21,22]

Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance.[23-25] In randomized studies, rifaximin was more effective than nonabsorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute hepatic encephalopathy.[26-39] Furthermore, with minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics with detrimental side effects.

In this phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted over a 6-month period, we evaluated the efficacy and safety of rifaximin, used concomitantly with lactulose, for the maintenance of remission from episodes of hepatic encephalopathy in outpatients with a recent history of recurrent, overt hepatic encephalopathy.

## METHODS

### STUDY PATIENTS

Eligibility criteria were an age of at least 18 years, at least two episodes of overt hepatic encepha-

lopathy (Conn score, ≥2)[9,12] associated with hepatic cirrhosis during the previous 6 months, remission (Conn score, 0 or 1) at enrollment, and a score of 25 or less on the Model for End-Stage Liver Disease (MELD) scale[40] (on which scores can range from 6 to 40, with higher scores indicating more severe disease). Episodes of hepatic encephalopathy that were precipitated by gastrointestinal hemorrhage requiring transfusion of at least 2 units of blood, by medication use, by renal failure requiring dialysis, or by injury to the central nervous system were not counted as previous episodes.

Exclusion criteria included the expectation of liver transplantation within 1 month after the screening visit and the presence of conditions that are known precipitants of hepatic encephalopathy (including gastrointestinal hemorrhage and the placement of a portosystemic shunt or a transjugular intrahepatic portosystemic shunt) within 3 months before the screening visit, chronic renal insufficiency (creatinine level, >2.0 mg per deciliter [177 μmol per liter]) or respiratory insufficiency, anemia (hemoglobin level, <8 g per deciliter), an electrolyte abnormality (serum sodium level, <125 mmol per liter; serum calcium level, >10 mg per deciliter [2.5 mmol per liter]; or potassium level, <2.5 mmol per liter), intercurrent infection, or active spontaneous bacterial peritonitis. All patients or their legally authorized representatives provided written informed consent.

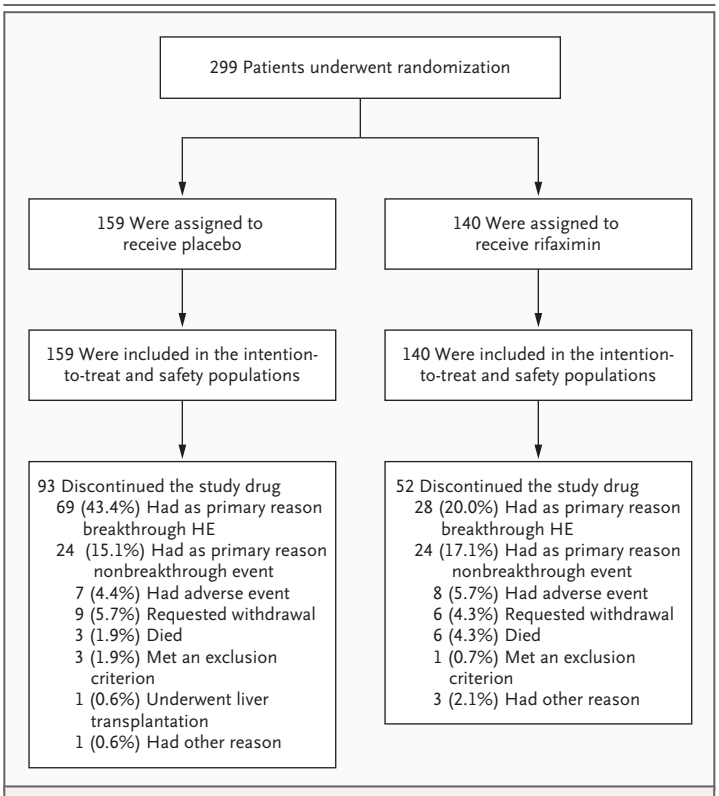



**Figure 1. Randomization and Follow-up of the Intention-to-Treat Population.**
HE denotes hepatic encephalopathy.

### STUDY DESIGN AND PROCEDURES

The protocol was approved by the institutional review board or ethics committee at each center and was conducted in accordance with International Conference on Harmonisation guidelines and other applicable laws and regulations. The study included a screening visit, an observation period between the screening visit and enrollment, and a 6-month treatment phase. On day 0, eligible patients were randomly assigned, in a 1:1 ratio, to receive either 550 mg of rifaximin or placebo, twice daily, for 6 months or until they discontinued the study drug because of a breakthrough episode of hepatic encephalopathy or another reason. Concomitant administration of lactulose was permitted during the study.

The study protocol was designed by representatives of Salix Pharmaceuticals and the academic authors. Data were collected by the principal investigators at each center (see the Appendix) and were monitored by Omnicare Clinical Research, Clinical Trial Management Services (now Chiltern International), and ClinStar Europe under the supervision of Salix representatives, who also analyzed the data. All authors participated in the interpretation of the data and the writing of the manuscript. An editorial consultant was paid by Salix to assist in the revision of subsequent drafts before submission. All authors vouch for the completeness and veracity of the data and data analyses.

### EFFICACY AND SAFETY ASSESSMENTS

Clinic visits occurred on days 7 and 14 and every 2 weeks thereafter through day 168 (end of the treatment period), with optional visits on days 42, 70, 98, 126, and 154. Patients were monitored by telephone during the weeks without clinic visits. Assessments included the Conn score and asterixis grade. Conn scores are defined as follows: 0, no personality or behavioral abnormality detected; 1, trivial lack of awareness, euphoria or anxiety, shortened attention span, or impairment of ability to add or subtract; 2, lethargy, disorientation with respect to time, obvious personality change, or inappropriate behavior; 3, somnolence

or semistupor, responsiveness to stimuli, confusion, gross disorientation, or bizarre behavior; and 4, coma.[9] Asterixis was assessed according to standard practice, by asking patients to extend their arms with wrists flexed backward and fingers open for 30 seconds or more.[11,39] Asterixis was then graded as follows: 0, no tremors; 1, few flapping motions; 2, occasional flapping motions; 3, frequent flapping motions; and 4, almost continuous flapping motions.[11] Investigators and site personnel who performed assessments were trained in order to ensure consistency across sites.

### STATISTICAL ANALYSIS

Efficacy data were analyzed for the intention-to-treat population, which included patients who received at least one dose of the study medication. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy, defined as the time from the first dose of the study drug to an increase from a baseline Conn score of 0 or 1 to a score of 2 or more or from a baseline Conn score of 0 to a Conn score of 1 plus a 1-unit increase in the asterixis grade. The key secondary efficacy end point was the time to the first hospitalization involving hepatic encephalopathy (defined as hospitalization because of the disorder or hospitalization during which an episode of hepatic encephalopathy occurred).

The Cox proportional-hazards model was used, with a 2-sided test and a significance level of 0.05, to compare the time to a breakthrough episode between the rifaximin group and the placebo group (after adjustment for geographic region). Kaplan–Meier methods were used to estimate the proportions of patients having a breakthrough episode at successive time points during the study. Patients who withdrew from the study early for

**Table 1. Baseline Characteristics of the Patients, According to Study Group.***

| Characteristic | Rifaximin (N=140) | Placebo (N=159) |
|---|---|---|
| Age — yr | 55.5±9.6 | 56.8±9.2 |
| Age group — no. (%) | | |
| <65 yr | 113 (80.7) | 128 (80.5) |
| ≥65 yr | 27 (19.3) | 31 (19.5) |
| Male sex — no. (%) | 75 (53.6) | 107 (67.3) |
| Race or ethnic group — no. (%)† | | |
| American Indian or Alaskan native | 5 (3.6) | 3 (1.9) |
| Asian | 4 (2.9) | 8 (5.0) |
| Black or of African ancestry | 7 (5.0) | 5 (3.1) |
| Native Hawaiian or Pacific Islander | 2 (1.4) | 1 (0.6) |
| White | 118 (84.3) | 139 (87.4) |
| Other | 3 (2.1) | 3 (1.9) |
| Missing data | 1 (0.7) | 0 |
| Duration of current remission — days | 68.8±47.7 | 73.1±51.3 |
| No. of HE episodes in past 6 mo — no. (%) | | |
| 2 | 97 (69.3) | 111 (69.8) |
| >2 | 43 (30.7) | 47 (29.6) |
| Missing data | 0 | 1 (0.6) |
| Conn score during most recent HE episode before study — no. (%)‡ | | |
| 1 | 1 (0.7) | 2 (1.3) |
| 2 | 115 (82.1) | 130 (81.8) |
| 3 or 4 | 23 (16.4) | 26 (16.4) |
| Missing data | 1 (0.7) | 1 (0.6) |
| Time since first diagnosis of advanced liver disease — mo | 51.2±49.2 | 60.5±64.9 |
| MELD score — no. (%)§ | | |
| ≤10 | 34 (24.3) | 48 (30.2) |
| 11–18 | 94 (67.1) | 96 (60.4) |
| 19–24 | 12 (8.6) | 14 (8.8) |
| Missing data | 0 | 1 (0.6) |

**Table 1. (Continued.)**

| Characteristic | Rifaximin (N=140) | Placebo (N=159) |
|---|---|---|
| Lactulose use at baseline — no. (%) | 128 (91.4) | 145 (91.2) |
| Concomitant medication use during the study — no. (%)¶ | | |
| Lactulose‖ | 128 (91.4) | 145 (91.2) |
| Spironolactone | 100 (71.4) | 100 (62.9) |
| Furosemide | 84 (60.0) | 94 (59.1) |
| Propranolol | 35 (25.0) | 35 (22.0) |
| Omeprazole | 29 (20.7) | 35 (22.0) |
| Pantoprazole | 25 (17.9) | 27 (17.0) |
| Ursodiol | 22 (15.7) | 22 (13.8) |
| Multivitamins | 21 (15.0) | 23 (14.5) |
| Folic acid | 20 (14.3) | 9 (5.7) |
| Esomeprazole magnesium | 20 (14.3) | 22 (13.8) |
| Nadolol | 16 (11.4) | 19 (11.9) |
| Acetaminophen | 14 (10.0) | 20 (12.6) |
| Insulin glargine | 12 (8.6) | 16 (10.1) |

* Plus–minus values are means ±SD. Differences between groups for each characteristic were tested for significance with Fisher's exact test for nominal variables and the t-test for continuous variables. Only sex and folic acid use differed significantly between groups (P=0.02 for each comparison). HE denotes hepatic encephalopathy.

† Race or ethnic group was self-reported.

‡ The Conn score can range from 0 to 4, with higher scores indicating more severe impairment.

§ The Model for End-Stage Liver Disease (MELD) score can range from 6 to 40, with higher scores indicating more severe disease.

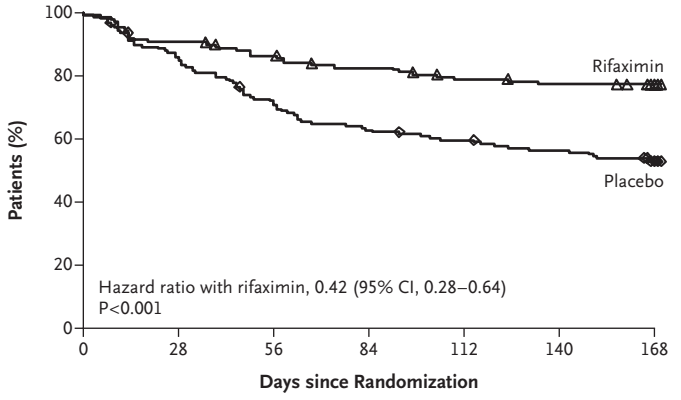
¶ The listed medications are those that were reportedly being used concomitantly with the study medication in 5% or more of patients in either group. Use of the following medications was prohibited during the study: benzodiazepines or benzodiazepine-like compounds, nonabsorbable disaccharides except lactulose, psyllium-containing intestinal regulators, warfarin-type anticoagulant agents, branched-chain amino acids, L-ornithine-L-aspartate, antibiotic therapy other than the study medication, and narcotic agents, psychotropic agents, and other psychoactive or neuroactive agents with the exception of gabapentin or pregabalin, sleep aids, and antihistamines used before the screening visit and administered at a constant dose throughout the study.

‖ Concomitant lactulose use (during the study) was coincidentally reported in the same number of patients as those reported to have been receiving lactulose at baseline. During the study, three of the patients who had been receiving lactulose discontinued the therapy, and another three patients started lactulose (one in the rifaximin group and two in the placebo group).

reasons other than the development of hepatic encephalopathy (e.g., another adverse event or the subject's request) were contacted 6 months after randomization to determine whether a breakthrough episode of hepatic encephalopathy had occurred since withdrawal. Data for patients who did not have breakthrough hepatic encephalopathy before day 168 were censored at the time of last contact or on day 168, whichever was earlier. Data for patients who did not have a hospitalization involving hepatic encephalopathy before day 168 were censored at the time of study termination or on day 168, whichever was earlier. The same statistical methods were used to analyze the key secondary end point: time to the first hospitalization involving hepatic encephalopathy.

The primary efficacy end point was evaluated in subgroups of patients according to the following characteristics: geographic region, sex, age, race or ethnic group, baseline MELD score, baseline Conn score, diabetes at baseline, duration of current verified remission, number of episodes of hepatic encephalopathy within the 6-month period before randomization, lactulose use at baseline, and previous placement of a transjugular intrahepatic portosystemic shunt.

Sample-size calculations were based on an assumption of breakthrough episodes of hepatic encephalopathy occurring in 50% and 70% of patients receiving rifaximin and placebo, respectively. These calculations indicated that to show the superiority of rifaximin over placebo with a statistical power of more than 80%, we would need to evaluate 100 patients per group. Safety data were



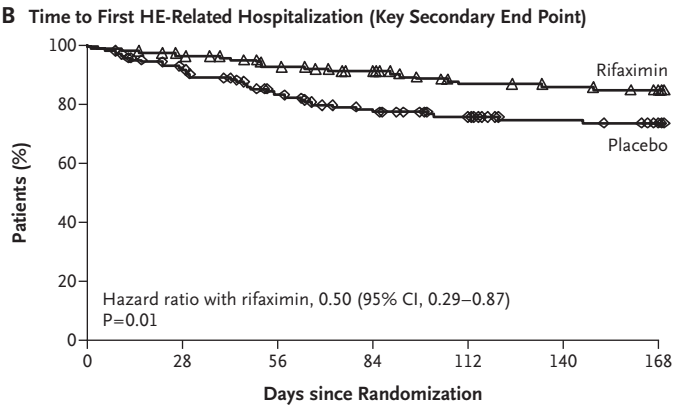




**Figure 2. Kaplan–Meier Estimates of the Primary and Key Secondary End Points in the Intention-to-Treat Population, According to Study Group.**

Symbols represent patients for whom data were censored. The P values were calculated by means of the log-rank test, with stratification according to geographic region. CI denotes confidence interval, and HE hepatic encephalopathy.

summarized with the use of descriptive statistics. Safety assessments included adverse events, serious adverse events, and adverse events specifically consisting of infection, including respiratory and gastrointestinal infections and their symptoms. Infections are of special interest because of known potential side effects of systemic antibiotics, as a drug class, and known effects of rifaximin.

## RESULTS

### STUDY PATIENTS

A total of 299 patients in the United States (205 patients), Canada (14 patients), and Russia (80 patients) were randomly assigned to receive a study drug at 70 investigative sites. The study began on December 5, 2005, and was completed on August 15, 2008. All patients received at least one dose of study medication and underwent at least one safety assessment after enrollment. Therefore, all patients were included in both the intention-to-treat population and the safety population (Fig. 1). As specified by the study protocol, the study drug was discontinued at the time of the first breakthrough episode of hepatic encephalopathy. The incidence of early withdrawal for any reason other than a breakthrough episode was similar in the rifaximin group and the placebo group.

Baseline characteristics were similar in the two groups (Table 1). Patients were predominantly white, male, and younger than 65 years of age. All patients had a history of overt episodic hepatic encephalopathy associated with advanced liver disease, diagnosed on the basis of two or more episodes of overt hepatic encephalopathy (Conn score, ≥2) within 6 months before the screening visit.

Similar percentages of patients in the placebo group (91.2%) and rifaximin group (91.4%) were receiving lactulose at baseline, and the mean daily doses of lactulose during the study period were stable (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Commonly used concomitant medications were those that would be expected for patients with chronic liver disease (Table 1).

The mean (±SD) duration of treatment was 130.3±56.5 days in the rifaximin group and 105.7±62.7 days in the placebo group. The rate of compliance, defined as use of at least 80% of the dispensed tablets, was high in both study groups (84.3% in the rifaximin group and 84.9% in the placebo group).

### BREAKTHROUGH EPISODES

Breakthrough episodes of hepatic encephalopathy were reported in 31 of 140 patients in the rifaximin group (22.1%) and 73 of 159 patients in the placebo group (45.9%). Figure 2A shows the time to a breakthrough episode (the primary end point). The hazard ratio for the risk of a breakthrough episode in the rifaximin group, as compared with the placebo group, was 0.42 (95% confidence interval [CI], 0.28 to 0.64; P<0.001), reflecting a relative reduction in the risk of a breakthrough episode by 58% with rifaximin as compared with placebo during the 6-month study period. These data suggest that four patients would need to be treated with rifaximin for 6 months to prevent one episode of overt hepatic encephalopathy. The degree to which rifaximin reduced the risk of a breakthrough episode was consistent across subgroups (Fig. 3).

| Subgroup | Rifaximin (N=140) | Placebo (N=159) | P Value for Treatment Effect |
|---|---|---|---|
| | *no. of patients* | | |
| Region | | | |
| United States and Canada | 101 | 118 | <0.001 |
| Russia | 39 | 41 | 0.03 |
| Sex | | | |
| Male | 75 | 107 | 0.009 |
| Female | 65 | 52 | <0.001 |
| Age | | | |
| <65 yr | 113 | 128 | <0.001 |
| ≥65 yr | 27 | 31 | 0.01 |
| Race or ethnic group | | | |
| White | 118 | 139 | <0.001 |
| Other | 22 | 20 | 0.046 |
| MELD score | | | |
| ≤10 | 34 | 48 | 0.01 |
| 11–18 | 94 | 96 | <0.001 |
| 19–24 | 12 | 14 | 0.21 |
| Conn score | | | |
| 0 | 93 | 107 | 0.002 |
| 1 | 47 | 52 | 0.003 |
| Lactulose use at baseline | | | |
| Yes | 128 | 145 | <0.001 |
| No | 12 | 14 | 0.33 |
| Diabetes | | | |
| Yes | 44 | 56 | 0.01 |
| No | 96 | 103 | <0.001 |
| Duration of remission | | | |
| ≤90 Days | 100 | 110 | <0.001 |
| >90 Days | 39 | 48 | 0.04 |
| No. of HE episodes in previous 6 mo | | | |
| 2 | 97 | 111 | 0.002 |
| >2 | 43 | 47 | 0.003 |
| TIPS | | | |
| Yes | 12 | 20 | 0.03 |
| No | 128 | 139 | <0.001 |
| Time to first breakthrough HE episode | 140 | 159 | <0.001 |

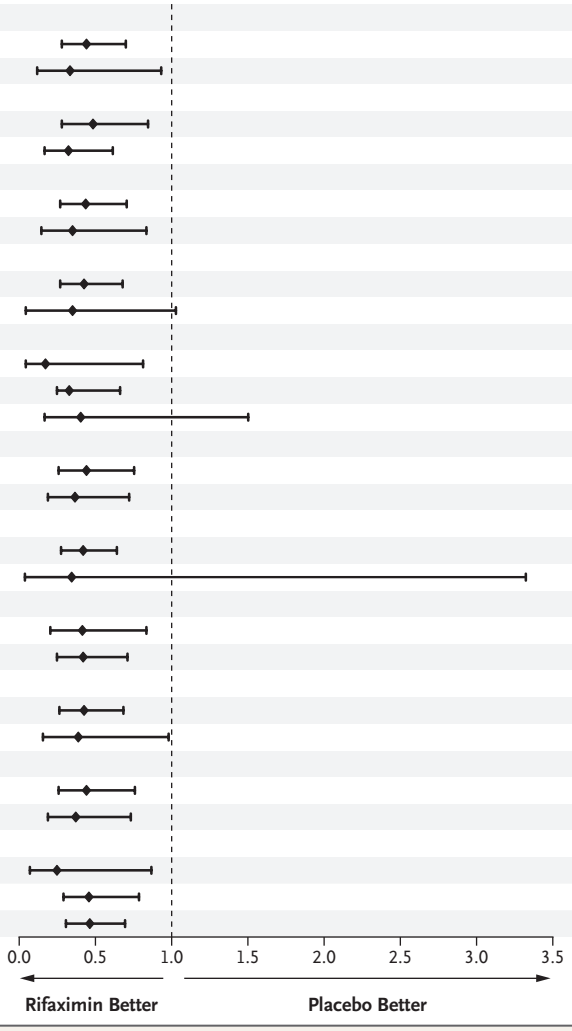



**Figure 3. Results of the Subgroup Analysis.**

Hazard ratios for the risk of a breakthrough episode of hepatic encephalopathy (HE) during the 6-month study period are shown for the rifaximin group, as compared with the placebo group, for various subgroups. The Model for End-Stage Liver Disease (MELD) score can range from 6 to 40, with higher scores indicating more severe disease. The Conn score can range from 0 to 4, with higher scores indicating more severe impairment. The P values were calculated by means of the log-rank test. Race or ethnic group was self-reported. TIPS denotes transjugular intrahepatic portosystemic shunt.

### HOSPITALIZATIONS

Hospitalization involving hepatic encephalopathy was reported for 19 of 140 patients in the rifaximin group (13.6%) and 36 of 159 patients in the placebo group (22.6%). The hazard ratio for the risk of such hospitalization in the rifaximin group, as compared with the placebo group, was 0.50 (95% CI, 0.29 to 0.87; P=0.01), reflecting a reduction in the risk by 50% with rifaximin as compared with placebo (Fig. 2B). Thus, nine patients would need to be treated with rifaximin for 6 months to prevent one hospitalization involving hepatic encephalopathy.

### SAFETY

The incidence of adverse events reported during the study was similar in the rifaximin group (80.0%) and the placebo group (79.9%), as was the incidence of the more common serious adverse events (Table 2). Among the adverse events related

to infection, *Clostridium difficile* infection was reported in two patients in the rifaximin group and none in the placebo group; both affected patients had several concurrent risk factors for *C. difficile* infection, such as advanced age, numerous recent hospitalizations involving multiple courses of antibiotic therapy, and use of the proton-pump inhibitor pantoprazole. In both patients, rifaximin therapy was continued concomitantly with treatment for the infection, from which they fully recovered.

A total of 20 patients died during the study (9 in the rifaximin group and 11 in the placebo group). Most of the deaths were attributed to conditions associated with disease progression: five patients in each of the two groups had hepatic cirrhosis, decompensated cirrhosis, hepatic failure, alcoholic cirrhosis, or end-stage liver failure, and two patients in each of the two groups had esophageal varices or hemorrhage from esophageal varices. Nearly all the patients who died had had evidence at baseline, apart from hepatic encephalopathy, of decompensated liver cirrhosis (i.e., portal hypertension, ascites or edema, or jaundice), which is associated with a reduced probability of survival.[41,42]

## DISCUSSION

The prevention of episodes of hepatic encephalopathy is an important goal in the treatment of patients with liver disease,[1,2,4,6,7] especially since symptoms of overt encephalopathy are debilitating and decrease the ability for self-care, leading to improper nutrition and nonadherence to a therapeutic regimen, which in turn leads to severe symptoms, frequent hospitalizations, and a poor quality of life. Our study showed that the use of rifaximin reduced the risk of a breakthrough episode of hepatic encephalopathy during a 6-month

**Table 2. Adverse Events, According to Study Group.***

| Event | Rifaximin (N=140) | Placebo (N=159) |
|---|---|---|
| | *number (percent)* | |
| **Adverse events†** | | |
| Any event | 112 (80.0) | 127 (79.9) |
| Nausea | 20 (14.3) | 21 (13.2) |
| Diarrhea | 15 (10.7) | 21 (13.2) |
| Fatigue | 17 (12.1) | 18 (11.3) |
| Peripheral edema | 21 (15.0) | 13 (8.2) |
| Ascites | 16 (11.4) | 15 (9.4) |
| Dizziness | 18 (12.9) | 13 (8.2) |
| Headache | 14 (10.0) | 17 (10.7) |
| Muscle spasms | 13 (9.3) | 11 (6.9) |
| Pruritus | 13 (9.3) | 10 (6.3) |
| Abdominal pain | 12 (8.6) | 13 (8.2) |
| Abdominal distention | 11 (7.9) | 12 (7.5) |
| Anemia | 11 (7.9) | 6 (3.8) |
| Vomiting | 10 (7.1) | 14 (8.8) |
| Insomnia | 10 (7.1) | 11 (6.9) |
| Depression | 10 (7.1) | 8 (5.0) |
| Cough | 10 (7.1) | 11 (6.9) |
| Constipation | 9 (6.4) | 10 (6.3) |
| Upper abdominal pain | 9 (6.4) | 8 (5.0) |
| Pyrexia | 9 (6.4) | 5 (3.1) |
| Back pain | 9 (6.4) | 10 (6.3) |
| Arthralgia | 9 (6.4) | 4 (2.5) |
| Dyspnea | 9 (6.4) | 7 (4.4) |
| Urinary tract infection | 8 (5.7) | 14 (8.8) |
| Rash | 7 (5.0) | 6 (3.8) |
| Asthenia | 4 (2.9) | 12 (7.5) |

**Table 2. (Continued.)**

| Event | Rifaximin (N=140) | Placebo (N=159) |
|---|---|---|
| | *number (percent)* | |
| **Serious adverse events‡** | | |
| Anemia | 4 (2.9) | 0 |
| Ascites | 4 (2.9) | 4 (2.5) |
| Esophageal varices | 4 (2.9) | 2 (1.3) |
| Pneumonia | 4 (2.9) | 1 (0.6) |
| Vomiting | 3 (2.1) | 0 |
| Generalized edema | 3 (2.1) | 2 (1.3) |
| Hepatic cirrhosis | 3 (2.1) | 6 (3.8) |
| Cellulitis | 3 (2.1) | 2 (1.3) |
| Acute renal failure | 2 (1.4) | 4 (2.5) |
| **Adverse events possibly related to infection§** | | |
| Bacterial peritonitis | 2 (1.4) | 4 (2.5) |
| Pneumonia | 4 (2.9) | 1 (0.6) |
| Gastrointestinal hemorrhage | 1 (0.7) | 3 (1.9) |
| Hematochezia | 2 (1.4) | 1 (0.6) |
| Bacteremia | 1 (0.7) | 2 (1.3) |
| Gastritis | 2 (1.4) | 0 |
| *Clostridium difficile* infection | 2 (1.4) | 0 |
| Sepsis | 0 | 2 (1.3) |

* The incidences of adverse events did not differ significantly between the two study groups (P>0.05 for all comparisons), according to Fisher's exact test.
† The adverse events listed were reported in 5% or more of the patients in either study group.
‡ The serious adverse events listed were reported in 2% or more of the patients in either study group (hepatic encephalopathy not included).
§ The adverse events possibly related to infection that are listed were reported in two or more patients in either study group. These were of special interest because of known potential side effects of the use of systemic antibiotics, as a drug class, and known effects of rifaximin.

period among patients in remission who had a recent history of recurrent overt hepatic encephalopathy (≥2 episodes within the previous 6 months) before enrollment. The reduced risk was seen across subgroups, further showing the consistency of the results, which expand previously reported findings of the efficacy of rifaximin in the treatment of overt hepatic encephalopathy.[26-34,39]

The current study differs from previous randomized studies in that it examined the protective effect of rifaximin against breakthrough episodes of hepatic encephalopathy rather than its effect in the treatment of acute, overt symptoms; the study also involved a larger group of patients and a longer study period. In previous randomized studies, rifaximin was administered for 21 days or less[26-30,32,33] or intermittently, for 14 or 15 days per month for 3 or 6 months.[33,34,39]

Our study shows the superiority of rifaximin therapy over treatment with lactulose alone. More than 90% of patients received concomitant lactulose during the study period, and a significant treatment effect was noted within 28 days after randomization. In contrast, a recent single-center, open-label study of 120 patients showed that although lactulose therapy was more effective than no active treatment in the prevention of overt hepatic encephalopathy,[15] the treatment effects favoring lactulose were apparent only after approximately 4 months.

In the current, prospective study, rifaximin therapy reduced the risk of hospitalization involving hepatic encephalopathy, reflecting the clinical significance of our efficacy findings. Also, the reduced risk of hospitalization supports the results of retrospective chart reviews,[4,43] which have shown that rifaximin, as compared with lactulose, is associated with a significantly lower frequency and duration of hospitalization and lower hospital costs.

The incidences of adverse events in general and adverse events consisting of infection in particu-

lar were similar in the rifaximin group and the placebo group. The safety profile of rifaximin appears to be superior to that of systemic antibiotics, particularly for patients with liver disease.[31] The occurrence of nephrotoxicity and ototoxicity with the use of aminoglycosides (e.g., neomycin and paromomycin) and of nausea and peripheral neuropathy with prolonged use of metronidazole restricts their use in patients with hepatic encephalopathy.[19,21,22]

The risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics. Plasma levels of rifaximin are negligible; therefore, bacteria outside the gastrointestinal tract are not exposed to appreciable selective pressure. In addition, whereas resistance to other antimicrobial agents is plasma-mediated, resistance to rifaximin is mediated through reversible genomic change. For chromosomally mediated mutation and selection to result in clinically relevant resistance, the mutation cannot be lethal and cannot significantly decrease virulence; otherwise, the resistant trait will not be transmitted. Both in vitro and in vivo studies of the effects of rifaximin on commensal flora suggest that rifaximin-resistant organisms have low viability.[25,44,45]

In summary, this study shows a robust protective effect of rifaximin against episodes of hepatic encephalopathy. Rifaximin also reduces the risk of hospitalization involving hepatic encephalopathy.[1,31]

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## APPENDIX

In addition to the authors, the following investigators participated in this study: Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod, Russia — O. Alexeeva; University of California, San Diego, Liver Center, San Diego — E. Alpert; Moscow Medical Academy, Moscow — V. Ananchenko; Albert Einstein Medical Center, Philadelphia — V. Araya; Dartmouth–Hitchcock Medical Center, Lebanon, NH — B. Berk; Gastroenterology Clinic, Monroe, LA — B. Bhandari; Center for Liver Disease and Transplantation, Columbia University Medical Center, New York — R. Brown; City Clinical Hospital #24, Moscow — E. Burnevich; University of Calgary Department of Medicine Health Sciences Center, Calgary, AB, Canada — K. Burak; Portage Regional Gastroenterology, Ravenna, OH — M. Cline; Vancouver Island Health Research Center, Victoria, BC, Canada — D. Daly; University of Colorado Health Science Center, Denver — L. Forman; Kansas City Gastroenterology and Hepatology, Kansas City, MO — B. Freilich; Royal Victoria Hospital, Montreal — P. Ghali; Clinic of Modern Medicine, Moscow — V. Gorbakov; Mount Sinai School of Medicine Recanti–Miller Transplant Institute, New York — P. Grewal; Charlotte Gastroenterology and Hematology, Charlotte, NC — J. Hanson; Long Beach Veterans Affairs (VA) Medical Center, Long Beach, CA — M. Jamal; Houston Digestive Diseases, Houston — S. Khan; University of Washington, Seattle — A. Larson; Alamo Medical Research, San Antonio, TX — E. Lawitz; Russian Academy of Advanced Medical Education of Roszdrav, Moscow — I. Loranskaya; University of Wisconsin Medical School, Madison — M. Lucey; Banner Good Samaritan Medical Center Liver Disease Center, Phoenix, AZ — R. Manch; Christus Transplant Institute, San Antonio, TX — R. McFadden; University of Rochester Medical Center, Rochester, NY — B. Maliakkal; Kirklin Clinic, Birmingham, AL — B. McGuire; Medical Company Hepatolog, Samara, Russia — V. Morozov; ClinBio Research Corporation, Merced, CA — S. Munnangi; Rayzan Regional Clinical Hospital, Ryazan, Russia — A. Nizov; Gastrointestinal Specialists of Clarksville, Clarksville, TN — A. Patel; Gastroenterology and Hepatology Clinic, Abbotsford, BC, Canada — H. Pluta; Brigham and Women's Hospital, Boston — A. Qamar; Smolensk Regional Clinical Hospital, Smolensk, Russia — V. Rafalsky; University of California Davis Medical Center, Sacramento — L. Rossaro; Metropolitan Research, Fairfax, VA — V. Rustgi; Froedtert Memorial Lutheran Hospital, Milwaukee — K. Saeian; VA Medical Center, Iowa City, IA — W. Schmidt; Gastroenterology Associates of Central Georgia, Macon — S. Sedghi; Transplant Unit, Washington, DC — K. Shetty; Saratov State Medical University of Roszdrav, Saratov, Russia — Y. Shvarts; University Internal Medicine Specialists, Detroit — F. Siddiqui; City Clinical Hospital Sergey Petrovich Botkin, Moscow — T. Sotnikova; University of Vermont College of Medicine Digestive Diseases Center, Burlington — D. Strader; Mayo Clinic Rochester, Rochester, MN — J. Talwalkar; Concorde Medical Group, New York — H. Tobias; Permian Research Foundation, Odessa, TX — R. Vemuru; City Hospital of St. Reverend Martyr Elizabeth, St. Petersburg, Russia — N. Volga; Infections Clinical Hospital #2, Moscow — E. Voltchkova; New York Medical College, Valhalla — D. Wolf; City Infections Hospital #30 Sergey Petrovich Botkin, St. Petersburg, Russia — A. Yakovlev; Carolina Center for Clinical Trials, University of North Carolina School of Medicine, Chapel Hill — S. Zacks; Center to Prevent and Fight the Acquired Immunodeficiency Syndrome and Infectious Diseases, St. Petersburg, Russia — N. Zakharova.

## REFERENCES


1. Poordad FF. The burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007;25:Suppl 1:3-9.
2. Munoz SJ. Hepatic encephalopathy. Med Clin North Am 2008;92:795-812.
3. Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:95-110.
4. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. Dig Dis Sci 2007;52:737-41.
5. Kalaitzakis E, Josefsson A, Björnsson E. Type and etiology of liver cirrhosis are not related to the presence of hepatic encephalopathy or health-related quality of life: a cross-sectional study. BMC Gastroenterol 2008;8:46.
6. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30:890-5.
7. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver Transpl 2007;13:1366-71.
8. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy — definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology 2002;35:716-21.
9. Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins, 1979.
10. Córdoba J, Blei AT. Hepatic encephalopathy. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's diseases of the liver. 10th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2007:569-99.
11. Williams R, James OF, Warnes TW, Morgan MY. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multi-centre study. Eur J Gastroenterol Hepatol 2000;12:203-8.
12. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy: a double blind controlled trial. Gastroenterology 1977;72:573-83.
13. Córdoba J, Mínguez B. Hepatic encephalopathy. Semin Liver Dis 2008;28:70-80.
14. Blei AT, Córdoba J. Hepatic encephalopathy. Am J Gastroenterol 2001;96:1968-76.
15. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137:885-91.
16. Morgan MY, Blei A, Güngreiff K, et al. The treatment of hepatic encephalopathy. Metab Brain Dis 2007;22:389-405.
17. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004;328:1046.
18. Bass NM. The current pharmacological therapies for hepatic encephalopathy. Aliment Pharmacol Ther 2007;25:Suppl 1:23-31.
19. Tierney LM Jr, McPhee SJ, Papadakis MA, eds. Current medical diagnosis & treatment. 38th ed. Stamford, CT: Appleton & Lange, 1999:1453-5.
20. Durante-Mangoni E, Grammatikos A, Utili R, Falagas ME. Do we still need the aminoglycosides? Int J Antimicrob Agents 2009;33:201-5.
21. Leitman PS. Liver disease, aminoglycoside antibiotics and renal dysfunction. Hepatology 1988;8:966-8.
22. Hampel H, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. Am J Gastroenterol 2001;96:2206-10.
23. Gerard L, Garey KW, DuPont HL. Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. Expert Rev Anti Infect Ther 2005;3:201-11.
24. Jiang ZD, DuPont HL. Rifaximin: in vitro and in vivo antibacterial activity — a review. Chemotherapy 2005;51:Suppl 1:67-72.
25. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. J Chemother 2008;20:186-94.
26. Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. Curr Med Res Opin 1993;13:109-18.
27. Festi D, Mazzella G, Orsini M, et al. Rifaximin in the treatment of chronic hepatic encephalopathy: results of a multicenter study of efficacy and safety. Curr Ther Res Clin Exp 1993;54:598-609.
28. Puxeddu A, Quartini M, Massimetti A, Ferrieri A. Rifaximin in the treatment of chronic hepatic encephalopathy. Curr Med Res Opin 1995;13:274-81.
29. Paik YH, Lee KS, Han KH, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Med J 2005;46:399-407.
30. Mas A, Rodés J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol 2003;38:51-8.
31. Loguercio G, Federico A, De Girolamo V, Ferrieri A, Del Vecchio Blanco C. Cyclic treatment of chronic hepatic encephalopathy with rifaximin: results of a double-blind clinical study. Minerva Gastroenterol Dietol 2003;49:53-62.
32. Pedretti G, Calzetti C, Missale G, Fiaccadori F. Rifaximin versus neomycin on hyperammoniemia in chronic portal systemic encephalopathy of cirrhotics: a double-blind, randomized trial. Ital J Gastroenterol 1991;23:175-8.
33. Di Piazza S, Gabriella Filippazzo M, Valenza LM, et al. Rifaximine versus neomycin in the treatment of portosystemic encephalopathy. Ital J Gastroenterol 1991;23:403-7.
34. Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy: a double-blind, randomised trial. Curr Med Res Opin 1997;13:593-601.
35. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol 2008;20:1064-70.
36. Lawrence KR, Klee JA. Rifaximin for the treatment of hepatic encephalopathy. Pharmacotherapy 2008;28:1019-32.
37. de Melo RT, Charneski L, Hilas O. Rifaximin for the treatment of hepatic encephalopathy. Am J Health Syst Pharm 2008;65:818-22.
38. Maclayton DO, Eaton-Maxwell A. Rifaximin for treatment of hepatic encephalopathy. Ann Pharmacother 2009;43:77-84.
39. Giacomo F, Francesco A, Michele N, Oronzo S, Antonella F. Rifaximin in the treatment of hepatic encephalopathy. Eur J Clin Res 1993;4:57-66.
40. Brown RS Jr, Kumar KS, Russo MW, et al. Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. Liver Transpl 2002;8:278-84.
41. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-31.
42. Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7:122-8.
43. Neff GW, Kemmer N, Zacharias VC, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. Transplant Proc 2006;38:3552-5.
44. DuPont HL, Jiang ZD. Influence of rifaximin treatment on the susceptibility of intestinal Gram-negative flora and enterococci. Clin Microbiol Infect 2004;10:1009-11.
45. Brigidi P, Swennen E, Rizzello F, Bozzolasco M, Matteuzzi D. Effects of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. J Chemother 2002;14:290-5.