Bears, beets, rifaximin

Peter L Wang MD¹, Jennifer A Flemming MD, MAS¹,²

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Author Affiliation

¹Department of Medicine, Queen’s University, Kingston, Ontario, Canada; ²Department of Public Health Sciences, Queen’s University, Kingston, Ontario, Canada

Correspondence: Jennifer A Flemming, Departments of Medicine and Public Health Sciences, Queen’s University, Kingston Health Sciences Centre – Hotel Dieu Hospital Site, 166 Brock Street, Kingston, Ontario K7L 5M2 Canada. Telephone: 613-544-3400, ext 2483. Fax: 613-544-3114. E-mail: jennifer.flemming2@kingstonhsc.ca

Riggio O, Masini A, Efrati C, et al. Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study. *J Hepatol*. 2005;42(5):674–679. doi:10.1016/j.jhep.2004.12.028

Bureau C, Thabut D, Jezequel C, et al. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Ann Intern Med*. 2021;174(5):633–640. doi:10.7326/M20-0202

Rifaximin and its effect on the gut are to gastroenterologists and hepatologists what “bears, beets, Battlestar Galactica” are to the character Dwight Schrute in the hit NBC show *The Office* – hardly a week goes by without them being invoked in his presence. Discovered in 1980 by Alfa Wasserman as a derivative of the rifamycin family of antibiotics, rifaximin has become a “Swiss Army knife” for gastroenterologists and hepatologists. Rifaximin is a broad-spectrum antimicrobial agent with effects against both aerobic and anaerobic gram-positive and gram-negative gut bacteria with negligible systemic absorption and few side effects or drug interactions (1). Its remarkable gut-specificity has thus been leveraged to treat numerous gastrointestinal disorders, including traveller’s diarrhea, small intestinal bowel overgrowth, irritable bowel syndrome, and hepatic encephalopathy (HE) (2).

The presumed mechanism of action by which rifaximin treats HE is through its ability to reduce harmful metabolites and endotoxins produced by the gut microbiome, as well as shifting the overall makeup of the gut flora. In the last 20 years, rifaximin has developed a well-established role in the secondary prevention of HE (3,4), yet surprisingly, its efficacy has not been supported for its use in primary prevention (5). One of the major risk factors for the development of HE is undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure, typically performed for complications of portal hypertension, including refractory ascites and variceal bleeding. TIPS predisposes
patients to HE, as it forcefully shunts blood (and thus toxins) away from the liver and prevents their removal. Given that up to 50% of individuals who receive TIPS develop HE and associated morbidity (6), there has been great interest in determining whether post-TIPS HE can be prevented.

Question: Can we prevent the incidence of HE in patients receiving TIPS?

There are basically two relevant prospective studies to review (7,8).

In 2005, a randomized control study by Riggio et al (7) looked at the rate of overt HE in patients with cirrhosis who took either rifaximin (1,200 mg/day), lactitol, or placebo immediately after TIPS. One-third of the patients had alcohol-associated liver disease, and two-thirds had bleeding as the indication for TIPS; the rest had ascites. No differences were observed in rates of incident HE with either rifaximin or lactitol at 1 month post-TIPS compared with placebo (32% versus 32% versus 36% respectively; \( p = 0.97 \)). As a result, rifaximin was not recommended for primary prevention of post-TIPS HE in the most recent 2014 North American and European guidelines (9) or Baveno VI group consensus (10). Recently, Bureau et al designed a randomized controlled trial that addressed the major limitations of the study by Riggio, including a rifaximin run-in period, longer follow-up post-TIPS, and a larger sample size with power to detect a smaller effect size between the groups. Published in the May 2021 issue of *Annals of Internal Medicine*, they provide new and compelling evidence for the efficacy of rifaximin in primary prevention of HE in patients undergoing elective TIPS (8).

This was a randomized, double-blind, multicentre, placebo-controlled trial in 12 tertiary care centres in France. Adult patients with cirrhosis who were scheduled for elective TIPS for the indication of refractory ascites or variceal bleeding prevention were recruited by their hepatologists. Individuals were excluded for typical contraindications, including having a Child–Pugh–Turcotte score \( >12 \), the presence of hepatocellular carcinoma beyond Milan criteria, and recurrent or persistent overt HE (a single episode of overt HE was allowed). Here, the authors defined overt encephalopathy as grade 2 or higher using West Haven criteria. Eligible patients were randomly assigned in blocks based on history of overt HE (yes versus no) and Child–Pugh score (A+B versus C) in a 1:1 ratio to either receive rifaximin 600 mg or placebo twice daily starting 14 days prior to TIPS and continuing up to 168 days after (\(-6\) months total). The primary outcome was the incidence of overt HE after TIPS, as just defined, which was evaluated at each regularly scheduled study visit or at the time of hospital admission for HE.

Between 2013 and 2016, 197 patients were recruited, with 97 assigned to the rifaximin arm and 100 to the placebo arm—nearly three times larger than the Riggio study—with 93 patients per arm actually going on to receive TIPS. Notably, most patients had alcohol-associated liver disease (86%) and received TIPS for refractory ascites (81%). Few patients had a history of overt HE (13%). In a modified intention to treat analysis (excluding those who did not receive TIPS, \( n = 8 \)), the incidence of HE up to 168 days post-TIPS was significantly lower in patients assigned to rifaximin than placebo (34% versus 53%; odds ratio 0.48, CI 0.27–0.87). There were no differences in the incidence of minimal HE (27% versus 29%, \( p = 0.74 \)), adverse events (93% versus 95%, \( p = 0.99 \)), or transplant-free survival (87% versus 81%, \( p = 0.27 \)) between rifaximin and placebo. There were no differences in any of the liver-related adverse events between treatment arms.

To review then, the study by Riggio et al suggests no benefit to rifaximin in primary prevention of post-TIPS HE, while the study by Bureau et al suggests rifaximin reduces the odds by \( >50\% \) (see Table 1). So where does this leave the practising clinician when deciding if their patients should receive rifaximin for primary HE prevention prior to TIPS? The important thing to recognize is that despite sharing similar patient populations (those receiving TIPS) and the same primary outcome (post-TIPS HE), these two studies have key differences in study population and study design that you will need to consider based on the patient in your care. The present study by Bureau et al mainly included patients who had alcohol-associated liver disease (\( >80\% \)) with a median MELD score of 12 compared with the study by Riggio et al, in which one-third had alcohol-associated disease, and the median MELD score was 9. Therefore, the population evaluated by Bureau may have had a higher predisposition to HE than those in the Riggio study. Further, the study by Bureau had a 14-day run-in period for rifaximin before receiving TIPS compared with the Riggio study, in which rifaximin was started post-TIPS and which is hypothesized to influence its efficacy. Moreover, as the authors explain, a
**Table 1: Comparison between studies**

| Study | Bureau et al | Riggio et al |
|-------|--------------|--------------|
| **Type** | Multi-centre double-blinded randomized controlled trial | Single centre unblinded randomized controlled trial |
| **Setting** | 12 sites in France, 2013–2016 | Single referral centre in Italy, 1993–2003 |
| **Inclusion** | Adult patients with cirrhosis for (1) prevention of recurrence of gastrointestinal bleeding related to portal hypertension, or (2) ascites or refractory hydrothorax | Adult patients with cirrhosis for (1) variceal bleeding and (2) refractory ascites |
| **Exclusion** | Child–Pugh score over 12, hepatocellular carcinoma beyond Milan criteria, recurrent or persistent overt HE defined as grade 2 or higher on the West Haven modified criteria | Non-cirrhotic portal hypertension |
| **Interventions** | 2 arms:  
• Rifaximin 600 mg twice daily  
• Placebo tabs twice daily  
Started 2 weeks prior to TIPS then for 6 months post TIPS | 3 arms:  
• Rifaximin 400 mg three times daily  
• Lactitol 20 mL three times daily  
• No treatment  
Started immediately post-TIPS |
| **Outcomes** | Primary: Overt HE within 168 days after TIPS  
Secondary: other liver disease-related complications, transplant-free survival | Overt HE within 1 month |
| **Power** | 89 per group for 80% power to detect a difference, assuming 17% and 35% have post-TIPS HE in the rifaximin and placebo group, respectively, accounting 5% loss to follow-up | 25 per group for 80% power to detect a difference, assuming 10% and 40% have post-TIPS HE in the treatment and no treatment group, respectively |
| **Length of follow-up** | 14 days pre- and 168 days post-TIPS  
At 0 day, 14 then every 28 days for 168 days, then every 3 months until 1 year, death, or liver transplant | 30 days, weekly outpatient visits |
| **Baseline characteristics** | N = 197  
Mean age (years): 60 ± 8  
Male: 77%  
Alcohol-associated liver disease: 86%  
MELD: 12 ± 4  
Ascites as indication: 81%  
Prior overt HE: 13%  
Post-TIPS PSG: 6 ± 2 mmHg | N = 75  
Mean age (years): 57 ± 11  
Male: 65%  
Alcohol-associated liver disease: 33%  
MELD: 9 ± 5  
Ascites as indication: 33%  
Prior overt HE: 15%  
Post-TIPS PSG: 7 ± 3 mmHg |
| **Key findings** | **Overt HE by 168 days:**  
Rifaximin: 32/93  
Placebo: 49/93  
**Cumulative incidence at 28 days:**  
Rifaximin: 22% (95% CI 13%–30%)  
Placebo: 32% (95% CI 22%–41%)  
**Cumulative incidence at 168 days:**  
Rifaximin: 35% (95% CI 25%–44%)  
Placebo: 56% (95% CI 43%–65%)  
p = 0.008 | **Overt HE by 30 days:**  
Rifaximin: 8/25  
Lactitol: 9/25  
No treatment: 8/25  
**Cumulative incidence at 30 days:**  
Graphical, value not reported  
p = 0.97  
**Multivariate analysis for risk factors for overt HE at 30 days:**  
Prior HE: HR 3.79 (95% CI 1.27–11.31)  
TMT-A Z score >1.5: HR 3.55 (95% CI 1.24–10.2) |
greater reduction in post-TIPS HE in the Bureau study occurred at 168 days (cumulative incidence 35% versus 56%) rather than 28 days; that is, 1 month (cumulative incidence 22% versus 32%), as was the follow-up time in the Riggio study. Finally, all patients in the Bureau study received elective TIPS, whereas, in the Riggio study, 20% of TIPS were for emergent indications and therefore comprised a much different patient population. Thus, taken together, these two studies are not at odds per se, as the benefit of rifaximin in the prevention of post-TIPS HE may depend on the type of “bear” you are dealing with (to return to our Office analogy). Even though a polar bear and panda bear are both, by definition, bears, you are not going to get the same outcome by placing a polar bear in a bamboo tree. Therefore, at present, the evidence for rifaximin in post-TIPS HE primary prevention is supported for elective procedures, mostly in patients with alcohol-associated disease with refractory ascites, and where you are able to administer rifaximin for 2 weeks prior to TIPS.

There are still many unknowns. The length of treatment post-TIPS is not clear, which is of clinical and economic relevance, as rifaximin’s cost remains prohibitive for uninsured patients in many countries. Also of interest is whether there is an additive or synergistic effect of lactulose with rifaximin when administered prior to TIPS in a larger randomized study than the one in 2005. Fortunately, there is an ongoing trial, the Prevention of hepatic Encephalopathy by Administration of Rifaximin and Lactulose (PEARL) study, which is evaluating the effectiveness of these agents co-administered 3 days pre- and 3 months post-TIPS.

Pending answers to some of these questions, the role of rifaximin in primary prophylaxis of post-TIPS HE is limited to a select patient population, although our fascination with this special, gut-localizing antimicrobial drug will certainly remain.

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