

# World Journal of *Hepatology*

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## Can rifaximin for hepatic encephalopathy be discontinued during broad-spectrum antibiotic treatment?

Chien-Hao Huang, Piero Amodio

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### Abstract

Hepatic encephalopathy (HE) is a formidable complication in patients with decompensated cirrhosis, often necessitating the administration of rifaximin (RFX) for effective management. RFX, is a gut-restricted, poorly-absorbable oral rifamycin derived antibiotic that can be used in addition to lactulose for the secondary prophylaxis of HE. It has shown notable reductions in infection, hospital readmission, duration of hospital stay, and mortality. However, limited data exist about the concurrent use of RFX with broad-spectrum antibiotics, because the patients are typically excluded from studies assessing RFX efficacy in HE. A pharmacist-driven quasi-experimental pilot study was done to address this gap. They argue against the necessity of RFX in HE during broad-spectrum antibiotic treatment, particularly in critically ill patients in intensive care unit (ICU). The potential for safe RFX discontinuation without adverse effects is clearly illuminated and valuable insight into the optimization of therapeutic strategies is offered. The findings also indicate that RFX discontinuation during broad-spectrum antibiotic therapy was not associated with higher rates of delirium or coma, and this result remained robust after adjustment in multivariate analysis. Furthermore, rates of other secondary clinical and safety outcomes, including ICU mortality and 48-hour changes in vasopressor requirements, were comparable. However, since the activity of RFX is mainly confined to the modulation of gut microbiota, its potential utility in patients undergoing extensive systemic antibiotic therapy is debatable, given the overlapping antibiotic activity. Further, this suggests that the action of RFX on HE is class-specific (related to its activity on gut microbiota), rather than drug-specific. A recent double-blind randomized controlled (ARiE) trial provided further evidence-based support for RFX withdrawal in critically ill cirrhotic ICU patients receiving broad-spectrum antibiotics. Both studies prompt further discussion about optimal therapeutic strategy for patients facing the dual challenge of HE and systemic infections.



Despite these compelling results, both studies have limitations. A prospective, multi-center evaluation of a larger sample, with placebo control, and comprehensive neurologic evaluation of HE is warranted. It should include an exploration of longer-term outcome and the impact of this protocol in non-critically ill liver disease patients.

**Key Words:** Rifaximin discontinuation; Hepatic encephalopathy; Broad-spectrum antibiotics; Critically ill; Medical intensive care unit; Pharmacist-driven protocol

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**Core Tip:** Rifaximin (RFX) is a gut-restricted adjunct to lactulose that minimizes hepatic encephalopathy (HE) recurrence with minimal systemic absorption. Despite established benefits, limited Food and Drug Administration approval for acute HE raises concern about its use in treating acute overt HE. Recent evidence challenges the routine use of RFX with broad-spectrum antibiotics, emphasizing their class-specific effects in critically ill patients. The study sheds light on the safety of discontinuing RFX during broad-spectrum antibiotic therapy in intensive care unit patients with liver disease and HE, and also prompts reevaluation of the role of RFX amid the overlapping antibiotic activity. This evidence underscores the need for further investigations to optimize the management of both HE and systemic infections in patients with liver disease, including those who are not critically ill.

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## INTRODUCTION

Hepatic encephalopathy (HE), a neuropsychiatric complication of decompensated cirrhosis, manifests across a clinical spectrum from minimal cognitive dysfunction to lethargy and coma[1,2]. It carries substantial mortality and recurrence risks[3] and impacts the health-related quality of life in cirrhotic patients to a significant degree[4]. Despite an incomplete understanding of the comprehensive mechanisms[3], pseudo-neurotransmitters like gamma-aminobutyric acid (GABA), ammonia, and indole are well-established neurotoxins implicated in HE[5,6]. It has been suggested that neurotoxins, such as the ammonia produced by colonic bacteria and enterocytes that metabolize proteins, enter the systemic circulation through the portal vein and blood-brain barrier, and contribute to neurologic dysfunction and HE under cirrhotic conditions[7]. The gastrointestinal tract serves as the primary source of ammonia, with growing a recognition of gut microbiota as another significant contributor. Current drug therapies for HE, such as lactulose and rifaximin (RFX), focus on the reduction of plasma ammonia levels and the improvement of gut dysbiosis.

RFX, which has very low systemic absorption, is used as an adjunctive to lactulose to prevent the recurrence of HE[3, 8]. This gut-restricted, non-absorbable rifamycin derived oral antibiotic, acts against ammonia-producing gram-positive, gram-negative, and anaerobic bacteria[9,10]. RFX demonstrates efficacy in preventing overt HE (OHE) recurrence and is linked to significant reduction in infections, hospital readmissions, and durations of hospital stay[11,12]. RFX actively improves the quality of life[13] and single-center studies suggest potential survival benefit for HE patients treated with RFX[12]. However, despite being frequently used for the prevention or treatment of acute HE[12], RFX still awaits Food and Drug Administration approval for the treatment of acute OHE due to the limited amount of supportive evidence[14].

Antibiotics, by acting on gut microbiota, reduce indole which can potentially be converted into the neurotoxic substance oxindole in the brain[15]. They also attenuate the inflammatory response driven by pathogen-associated molecular pattern molecules (PAMPS)/endotoxins[16] and may prevent the binding of GABA in the central nervous system[17]. Notably, proinflammatory interleukins, produced during infection or an inflammatory state interact with ammonia, and can contribute to alterations in brain function[18].

In the medical intensive care unit (MICU), where infection prevalence is high[19] and infection commonly acts as a precipitant of OHE in critically ill patients[20], individuals frequently receive RFX alongside broad-spectrum antibiotics. This practice persists despite the absence of endorsement in current practice guidelines for treating OHE in the presence of infection[14]. Therefore, Ward *et al*[21] conducted a study that addressed this crucial knowledge gap; they demonstrated that RFX can be safely discontinued without adverse effect in patients with severe liver disease and HE undergoing extensive broad-spectrum antibiotic treatment in the MICU. The implicit rationale of the study suggests that the beneficial effects of RFX in HE were mainly class-specific, not drug-specific.

A plethora of antibiotic treatments has demonstrated efficacy in treating HE, with the initial recognition of tetracyclines' utility in hepatic coma[22]. Subsequent investigations highlighted the crucial role of reducing microbiota activity to reverse HE, leading to the exploration of metronidazole[23] and other poorly absorbed antibiotics like vancomycin[24], neomycin[25], and RFX[26]. These agents were preferred due to their capacity to diminish or avoid unnecessary systemic effects, considering the frequent associated systemic toxicity. Particularly noteworthy is RFX, which, among other poorly absorbed oral antibiotics, exhibits a safer profile than aminoglycosides[27]. Importantly, the

development of bacterial resistance to RFX does not compromise the activity of other antibiotics[28].

Thus, the effect of antibiotics in HE is a class action[29] that is shared by the antibiotic RFX, which was found to have a profound activity on gut microbiota in the first study[30]. Later studies based on microbiome analysis found no remarkable RFX effect[31] and suggested that the effect could have been a modulation of gut microbiota metabolism. However, conclusions were driven by the analysis of the relative abundance of bacteria. Changes in the absolute microbiota burden, which is the determinant of microbiota metabolic effect, might have yielded different results. A recent elegant study by Eriksen *et al*[32] showed that RFX+ lactulose administration reduces the systemic inflow of ammonia by 20%, while the ammonia plasma level was poorly changed, thus suggesting that a single measure of fasting ammonia may be less accurate in estimating gut ammonia production in cirrhosis[32].

Considering that the mechanism of RFX action is mainly related to its positive modulation of the distorted gut microbiota profile and burden (bacterial overgrowth) in advanced cirrhosis, the possibility that its use might be useful in subjects undergoing massive systemic antibiotic use is not evident *a priori*, and overlapping spectra of antibiotic activity with broad-spectrum antibiotics are expected.

The Ward *et al*[21] study has several limitations. As a single-center study, its generalizability may be limited, and variations in patient populations across centers may impact external validity. Second, the retrospective data collection introduces inherent limitations, including incomplete or missing data, recall bias, and an inability to control for all confounding variables. Third, despite including both acute and chronic HE, the absence of subgroup analysis may limit result interpretation. Fourth, reliance on surrogate endpoints such as days alive and freedom from delirium and coma, instead of West-Haven grades, may introduce variability and might not fully capture the impact, especially in assessing acute HE episodes. Fifth, the study did not assess long-term outcomes or the sustained effects of withheld RFX therapy, which could underestimate the beneficial role of RFX. Sixth, despite generally balanced groups, observed baseline differences, such as norepinephrine requirements and race, may potentially confound results. Seventh, the study enrolled critically ill patients with liver disease, representing a spectrum from compensated cirrhosis to decompensated liver cirrhosis without analyzing their Model for end stage liver disease scores, which greatly impact prognoses.

## CONCLUSION

At any rate, data supporting the combination use of RFX with broad-spectrum antibiotics are limited, as patients on broad-spectrum antibiotics have generally been excluded from studies on RFX efficacy in HE. Therefore, the Ward *et al* [21] study has great merit, since it provides an evidence-based argument to justify RFX withdrawal in patients with cirrhosis who receive broad-spectrum antibiotic treatment. Further, this is in agreement with the recent article by Kulkarni *et al*[14], which does not show any advantage on HE in patients with or without RFX that are treated with other antibiotics. Thus, both articles provide empirical evidence as to what could have been assumed only *a priori* based on antibiotic action. Despite these compelling results, it is crucial to acknowledge limitations in these studies. A prospective, multi-center evaluation in a larger sample, with placebo control and comprehensive neurologic evaluations for HE, might be useful. Additionally, exploring the impact of this protocol in non-critically ill liver disease patients should be considered.

## FOOTNOTES

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