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Lack of Colonic Microbial Cross-Resistance to Other Antibiotics in Patients Treated With Rifaximin Alone Versus Rifaximin Plus Lactulose for Reducing the Risk of Overt Hepatic Encephalopathy Recurrence

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INTRODUCTION

- Rifaximin is a nonsystemic antibiotic indicated for reduction in risk of overt hepatic encephalopathy (OHE) recurrence in adults[1]
  - Rifaximin 550 mg twice daily (BID) has been shown to reduce the relative risk of OHE recurrence by 58% (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.28-0.64; *P*<0.001) and to reduce the relative risk of hepatic encephalopathy (HE)-related hospitalization by 50% versus placebo (HR, 0.50; 95% CI, 0.29-0.87; *P*=0.01) during 6 months of treatment[2]
  - An analysis of a US Medicare population with cirrhosis reported that rifaximin treatment significantly decreased the risk of mortality after a diagnosis of HE (adjusted HR, 0.40; 95% CI, 0.39-0.42; *P*<0.001)[3]
  - Additionally, compared with no treatment, hospital days per person-year were lowest with rifaximin + lactulose (incident rate ratio [IRR], 0.28; 95% CI, 0.27-0.30) versus lactulose alone (IRR, 0.31; 95% CI, 0.30-0.32) or rifaximin alone (IRR, 0.49; 95% CI, 0.45-0.53)[3]
- Practice guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend rifaximin as add-on therapy to lactulose for the prevention of OHE recurrence[4]
- The risk of bacterial antibiotic resistance to rifaximin and cross-resistance to other antibiotics is thought to be low, possibly because of minimal systemic absorption,[5,6] and a requirement for a stable mutation in bacterial DNA (in contrast with plasmid-based mechanisms)[7]; data suggest that without selective pressure, resistant microorganisms do not effectively colonize the gastrointestinal tract in a clinical setting[8,9]
- Data are limited regarding the potential impact of concomitant lactulose on the bacterial susceptibility profile in patients with cirrhosis treated with rifaximin

OBJECTIVE

- To assess the effect of rifaximin + lactulose versus rifaximin alone on susceptibility of fecal bacteria to commonly used antibiotics in patients with cirrhosis and a history of OHE

METHODS

- Adults with cirrhosis and a history of ≥1 OHE episode during the previous 6 months, who were currently in HE remission (Conn score ≤1), were eligible for inclusion in a randomized, phase 4, open-label, active-controlled trial
  - Exclusion criteria included active spontaneous bacterial peritonitis or other current infection for which the patient was being treated with oral or parenteral antibiotics, and a positive stool test for *Clostridium difficile* (toxin A or B) at screening
- Patients were randomly assigned to receive open-label rifaximin 550 mg BID alone or rifaximin 550 mg BID + lactulose (titrated to 2-3 soft stools/d) for 6 months
  - Stool samples were collected at screening (baseline) and Month 6/end of treatment (EOT)
- Patients were randomly selected for the fecal microbiota antibiotic susceptibility substudy
- Bacteria were cultured using standard techniques
  - Susceptibility to several antibiotics, depending on bacterium, was tested by broth or agar dilution methods, and minimal inhibitory concentrations were determined
  - Previously defined breakpoints, if available, were used to determine resistance for the antibiotics tested[10]
  - Control strains were included per lab standard operating procedure practices
- Change from baseline in bacterial fractions was analyzed using 1-sample (within-treatment) or 2-sample (between-treatment) Wilcoxon tests on the log value (post-baseline bacterial fractions/baseline bacterial fractions) and corrected for multiple hypothesis testing via the Benjamini-Hochberg method

RESULTS

- The substudy included 64 patients (mean age, 55.8 y; 64.1% male; Table 1)

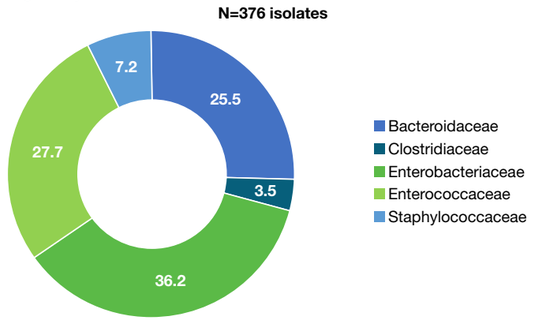
Table 1. Demographics and Baseline Characteristics

Parameter	Rifaximin 550 mg BID (n=31)	Rifaximin 550 mg BID + Lactulose (n=33)
Age, y, mean (SD)	56.2 (8.8)	55.4 (9.4)
Range	36–71	35–70
Male, n (%)	19 (61.3)	22 (66.7)
Race, n (%)		
White	30 (96.8)	30 (90.9)
Black	0	2 (6.1)
Other/unknown	1 (3.2)	1 (3.0)
Child-Pugh classification, n (%)		
Class A	16 (51.6)	11 (33.3)
Class B	15 (48.4)	21 (63.6)
Class C	0	1 (3.0)
MELD score, mean (SD)	10.6 (3.0)	11.8 (2.8)
Range	7–18	7–19

BID = twice daily; MELD = Model for End-Stage Liver Disease; SD = standard deviation.

- Overall, 376 bacterial isolates were identified in stool samples overall, with species of the Enterobacteriaceae, Enterococcaceae, and Bacteroidaceae families being the most frequently isolated (Figure; Table 2)

Figure. Fecal Bacterial Families Isolated in Stool Samples From 64 Patients During Study



- Stool samples from patients in each group had a similar distribution of bacterial families and species at baseline and EOT, and there were generally no differences in bacterial distribution between the 2 treatment groups and between the 2 timepoints (Table 2)
  - The most frequently identified bacterial species in the stool samples was *Escherichia coli* (24.7%; 93/376 isolates); all other species had a total frequency of ≤8.2%
- For *C difficile* and *Enterococcus faecalis*, there were fewer isolates recovered in stool samples post-treatment in the 2 treatment groups (Table 2)
- The number of *Enterococcus faecium* isolates in stool samples was generally similar at baseline (pre-treatment) and post-treatment in the 2 treatment groups

Table 2. Stool Bacterial Isolates Obtained During the Study

	Isolates, n (%)			
	Rifaximin 550 mg BID		Rifaximin 550 mg BID + Lactulose	
Microorganisms	Baseline (n=103)	EOT (n=80)	Baseline (n=92)	EOT (n=101)
Bacteroidaceae	21 (20.4)	23 (28.8)	22 (23.9)	30 (29.7)
Bacteroides fragilis	3 (2.9)	4 (5.0)	5 (5.4)	9 (8.9)
Bacteroides thetaiotaomicron	4 (3.9)	8 (10.0)	3 (3.3)	3 (3.0)
Bacteroides uniformis	4 (3.9)	2 (2.5)	6 (6.5)	7 (6.9)
Bacteroides vulgatus	5 (4.9)	4 (5.0)	4 (4.3)	5 (5.0)
Parabacteroides distasonis	3 (2.9)	4 (5.0)	3 (3.3)	4 (4.0)
Other	2 (1.9)	1 (1.3)	1 (1.1)	2 (2.0)
Clostridiaceae*				
Clostridium difficile	7 (6.8)	1 (1.3)	4 (4.3)	1 (1.0)
Enterobacteriaceae	35 (34.0)	32 (40.0)	33 (35.9)	36 (35.6)
Escherichia coli	27 (26.2)	19 (23.8)	23 (25.0)	24 (23.8)
Klebsiella oxytoca	2 (1.9)	5 (6.3)	2 (2.2)	1 (1.0)
Klebsiella pneumoniae	5 (4.9)	6 (7.5)	8 (8.7)	11 (10.9)
Other	1 (1.0)	2 (2.5)	0 (0)	0 (0)
Enterococcaceae	30 (29.1)	18 (22.5)	29 (31.5)	27 (26.7)
Enterococcus avium	6 (5.8)	3 (3.8)	9 (9.8)	7 (6.9)
Enterococcus casseliflavus	3 (2.9)	3 (3.8)	3 (3.3)	2 (2.0)
Enterococcus durans	2 (1.9)	1 (1.3)	2 (2.2)	3 (3.0)
Enterococcus faecalis	10 (9.7)	1 (1.3)	7 (7.6)	4 (4.0)
Enterococcus faecium	7 (6.8)	9 (11.3)	8 (8.7)	7 (6.9)
Other	2 (1.9)	1 (1.3)	0 (0)	4 (4.0)
Staphylococcaceae	10 (9.7)	6 (7.5)	4 (4.3)	7 (6.9)
Staphylococcus aureus	5 (4.9)	0 (0)	3 (3.3)	2 (2.0)
Staphylococcus epidermidis	5 (4.9)	5 (6.3)	0 (0)	3 (3.0)
Other	0 (0)	1 (1.3)	1 (1.1)	2 (2.0)

**C difficile* was the only *Clostridium* species cultured and tested.
BID = twice daily; EOT = end of treatment.

- Overall, there were no significant differences in mean change from baseline to EOT in stool bacterial fractions within or between the 2 treatment groups for taxa present in ≥25% of the population analyzed (data not shown; *P*>0.05)
  - The only significant difference observed was in the change from baseline to EOT for Enterococcaceae fraction in the rifaximin + lactulose group (*P*=0.02 vs baseline)
- Cross-resistance to other antibiotics rarely developed (Table 3)
  - The one post-treatment, rifaximin-resistant *C difficile* isolate remained susceptible to vancomycin or fidaxomicin, which are 2 antibiotics commonly used to treat *C difficile* infections

Table 3. Susceptibility Profile of Bacteria to Various Antibiotics

	Resistant Isolates, n			
	Rifaximin 550 mg BID		Rifaximin 550 mg BID + Lactulose	
Antibiotic Tested*	Baseline	EOT	Baseline	EOT
Enterobacteriaceae	n=35	n=32	n=33	n=36
Ceftazidime	1	1	0	2
Ceftriaxone	1	1	1	3
Ciprofloxacin	4	3	3	4
Imipenem	0	0	0	0
Meropenem	0	0	0	0
Piperacillin/tazobactam	0	0	0	0
Enterococcaceae	n=30	n=18	n=29	n=27
Ceftazidime	26	16	23	23
Ceftriaxone	16	7	14	15
Ciprofloxacin	3	6	2	4
Imipenem	2	3	0	4
Meropenem	10	8	12	14
Piperacillin/tazobactam	2	3	2	6
Bacteroidaceae	n=21	n=23	n=22	n=30
Fidaxomicin	21	23	22	30
Metronidazole	0	0	0	0
Vancomycin	7	4	9	11
Staphylococcaceae	n=10	n=6	n=4	n=7
Ceftazidime	0	0	0	0
Ceftriaxone	0	0	0	0
Ciprofloxacin	2	3	2	1
Imipenem	0	0	0	0
Meropenem	0	0	0	0
Piperacillin/tazobactam	0	0	1	0
Clostridiaceae	n=7	n=1	n=4	n=1
Fidaxomicin	1	0	0	0
Metronidazole	0	0	0	0
Vancomycin	0	0	0	0

*All MIC values less than assigned breakpoint were considered susceptible. The assigned breakpoint was either the CLSI established breakpoint or, for antibiotics without a CLSI established breakpoint, the highest dilution that was tested.
BID = twice daily; CLSI = Clinical Laboratory Standards Institute; EOT = end of treatment; MIC = minimal inhibitory concentration.

CONCLUSIONS

- **Rifaximin alone and rifaximin + lactulose for up to 6 months did not lead to clinically relevant changes to fecal microbial antibiotic susceptibility profiles**
  - **There was no indication of clinically relevant antibiotic resistance with the addition of lactulose to rifaximin therapy for the prevention of OHE recurrence**
- **These data support the clinical safety profile of rifaximin + lactulose in adults with cirrhosis and a history of OHE**

REFERENCES: **1.** Xifaxan® (rifaximin) tablets, for oral use [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2019. **2.** Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081. **3.** Tapper EB, et al. *Aliment Pharmacol Ther*. 2020;51(12):1397-1405. **4.** Vilstrup H, et al. *Hepatology*. 2014;60(2):715-735. **5.** Taylor DN, et al. *Antimicrob Agents Chemother*. 2008;52(3):1179-1181. **6.** Descombe JJ, et al. *Int J Clin Pharmacol Res*. 1994;14(2):51-56. **7.** Kothary V, et al. *Antimicrob Agents Chemother*. 2013;57(2):811-817. **8.** De Leo C, et al. *Drugs Exp Clin Res*. 1986;12(12):979-981. **9.** Brigidi P, et al. *J Chemother*. 2002;14(3):290-295. **10.** Clinical Laboratory Standards Institute. CLSI document M100-S24. Wayne, PA: CLSI; 2014.

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