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# Real-world evidence of long-term survival and healthcare resource use in patients with hepatic encephalopathy receiving rifaximin- $\alpha$ treatment: a retrospective observational extension study with long-term follow-up (IMPRESS II)

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## ABSTRACT

**Objective** To describe survival of patients with hepatic encephalopathy (HE), up to 5 years after initiation of rifaximin- $\alpha$  (RFX) treatment.

**Design/Method** A retrospective, observational extension study within 9 National Health Service secondary/tertiary UK care centres. All patients had a clinical diagnosis of HE, were being treated with RFX and were included in the previous IMPRESS study which reported the 1-year experience. Demographics, clinical outcomes, selected cirrhosis-related complications, hospital admissions and attendances up to 5 years from RFX initiation were extracted from patient medical records and hospital electronic databases. The primary outcome measure was survival at 5 years post-initiation of RFX treatment.

**Results** The study included 138 patients. The survival rate at 5 years post-initiation of RFX was 35% (95% CI 28.2% to 44.4%) overall and 36% (95% CI 26.1% to 45.4%) for patients with alcohol-related liver disease. Median survival from RFX initiation was 2.8 years (95% CI 2.0 to 3.8; n=136). Among 48 patients alive at 5 years, 69% remained on RFX treatment at the end of the observation period, 74% reported no cirrhosis-related complications and 24% (9/37) had received a liver transplant. Between 1 and 5 years post-initiation, total

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A number of studies have suggested that rifaximin- $\alpha$  (RFX) may improve survival, but these results remain to be confirmed in longer term multicentre studies.

## WHAT THIS STUDY ADDS

- ⇒ This is the first UK real-world study to evidence the long-term survival rate of patients with hepatic encephalopathy (HE) up to 5 years after initiating treatment with RFX.
- ⇒ Yearly survival rates after initiation of RFX appear improved in comparison to those previously published for HE.
- ⇒ In patients surviving 5 years after RFX initiation, treatment appeared well tolerated with most patients remaining on treatment at the end of the observation period.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results reported here support the long-term use and tolerability of RFX in patients with HE and will provide clinical decision-makers with further evidence of the continued benefits of RFX to improve clinical care.

numbers of liver-related emergency department visits, inpatient admissions, intensive care unit admissions and outpatient visits were 84, 194, 3 and 709, respectively; the liver-related 30-day readmission rate was 37%.

**Conclusion** Within UK clinical practice, RFX use in HE was associated with a 35% survival rate with high treatment adherence, 76% transplant-free survival rate, minimal healthcare resource and low rates of complications at 5 years post-initiation.

## INTRODUCTION

Hepatic encephalopathy (HE), a frequent complication of cirrhosis, is associated with significant morbidity and mortality rates higher than other hepatic decompensation events.<sup>1–3</sup> HE manifests as a spectrum of neuropsychiatric abnormalities with a significant socioeconomic burden for patients and caregivers.<sup>4</sup> Episodes of overt HE (displaying obvious clinical symptoms) occur in approximately 30%–40% of patients with cirrhosis, often require hospitalisation and can be triggered by infection, gastrointestinal bleeding or surgery.<sup>2–6</sup> Patients not effectively treated after their first episode have an increased risk of readmission, ongoing symptoms, complications and mortality.<sup>7</sup> Treatments for overt HE aim to resolve such episodes and prevent recurrence.<sup>2</sup> Previous studies have reported a 1-year survival probability in patients with HE of 36%–48.3%,<sup>1,8–10</sup> reducing to 23% by year 3<sup>8</sup> and 15% by year 5.<sup>1</sup>

Rifaximin- $\alpha$  (RFX) is a minimally absorbed oral antibiotic licensed for the reduction in recurrence of episodes of overt HE and was recommended by the National Institute for Health and Care Excellence for routine use in the UK National Health Service (NHS) in 2015.<sup>11</sup> The action of RFX is focused within the gut where it reduces ammonia-producing bacteria, improves antimicrobial activity and promotes gut barrier repair.<sup>12–13</sup> The efficacy and safety of RFX was evaluated in a meta-analysis of 28 randomised controlled trials (RCTs) of RFX versus other active drugs or placebo for patients with HE. In that analysis, RFX was shown to significantly reduce HE grade, improve cognitive impairment and reduce recurrent episodes but no significant improvement in mortality was observed.<sup>14</sup> Follow-up lengths for the included RCTs ranged from 3 days to 6 months, leaving the long-term effect of RFX treatment on survival unclear.<sup>14</sup>

RFX has been shown to reduce healthcare use for patients receiving RFX treatment in multiple studies,<sup>3–15–19</sup> but the relationship between RFX and mortality remains unclear. There is currently a lack of real-world data on the long-term survival of patients with HE receiving RFX in routine clinical settings. IMPRESS-II is an extension study in a subgroup of patients from the IMPRESS study that aimed to evaluate 5-year survival outcomes of RFX treatment in patients with HE in real-world settings.<sup>17</sup>

## MATERIALS AND METHODS

### Study design

IMPRESS-II was a retrospective observational study conducted in 9 of the 13 UK NHS centres included in IMPRESS.<sup>17</sup> The study population consisted of patients with a clinical diagnosis of HE and who were treated with RFX. Patients were eligible for inclusion in IMPRESS-II if they were included in the original IMPRESS study<sup>17</sup>; patients whose hospital records were unavailable were excluded. As this was a retrospective observational study and patient-level data were collected by members of the direct care team, there was no requirement for patient consent.

### Study objectives, outcomes and data collection

The primary objective was to describe survival up to 5 years after RFX initiation (defined as the ‘index date’). Secondary objectives included: baseline demographics, clinical characteristics at baseline 2 and 5 years post-RFX initiation, RFX treatment patterns and healthcare resource use (HCRU) between 1 and 5 years post-RFX initiation. Clinical data included: Model for End-Stage Liver Disease (MELD)/Child-Pugh/Albumin-Bilirubin (ALBI) scores, disease history, RFX treatment and cirrhosis-related complications (these included variceal bleeding, spontaneous bacterial peritonitis (SBP), renal dysfunction/hepatorenal syndrome and infections). Baseline Child-Pugh and MELD scores were recorded within a window of  $\pm 1$  month from RFX initiation. Treatment patterns included: RFX discontinuation, reasons for discontinuation, and subsequent reinitiation and concomitant treatment. HCRU included: inpatient admissions including intensive care unit (ICU), length of stay including ICU, reasons for hospitalisations (using International Classification of Disease (ICD)-10 codes to identify liver-related and all-cause HCRU (online supplemental table 1)<sup>17</sup>; hospitalisations not including day cases), hospital visits (emergency department (ED), outpatient), inpatient, ICU and 30-day readmission rates. ALBI scores were included as an indication of disease severity, given the low number of MELD and Child-Pugh scores recorded in medical records during the observation period.<sup>20</sup>

Relevant data from the original IMPRESS database were included in IMPRESS-II. Additional pseudo-anonymised data were collected from patient medical records by members of the direct care team. Data collection and management for IMPRESS-II was carried out between March 2020 and October 2021.

### Statistical analyses

All analyses were descriptive in nature. Categorical variables are reported as number (percentage) and quantitative data as mean (SD) or median (IQR), as appropriate. Survival was analysed from the index date using the Kaplan-Meier (KM) method, with the event defined as death (all causes), reported as 5-year

survival rates. Median survival was also analysed (95% CIs, not including those lost to follow-up (n=136)). Patients who were alive at 5 years and those lost to follow-up at the end of the observation period were censored at the end of the observation period and on the date of last contact, respectively. Survival rates were also analysed for the subgroup of participants with alcohol-related liver disease (ARLD). For variables with missing data, analyses were performed using the available data; denominators are presented where data were missing. HCRU data are presented for patients who were alive and receiving RFX treatment at 1 year post-index. ALBI scores were calculated from bilirubin and albumin results using the following formula:  $ALBI = (\log_{10} \text{bilirubin } (\mu\text{mol/L}) \times 0.66) + (\text{albumin } (\text{g/L}) \times -0.0852)$ .<sup>20</sup>

## RESULTS

### Patient demographics and clinical characteristics

A total of 138 patients from 9 centres were included in the study. Table 1 summarises patient baseline characteristics, figure 1 shows the flow of patients through the study and table 2 summarises liver-related clinical characteristics at 1, 2 and 5 years post-index. Mean (SD) age at index was 60.9 (11.6) years, 38% (53/138) of patients were female, 79% (109/138) had an overt HE phenotype and 70% (96/138) had ARLD. In total, 16% (21/131) of patients had a transjugular intrahepatic portosystemic shunt (TIPSS) pre-index.

### Survival

Median survival from index was 2.8 (95% CI 2.0 to 3.8) years (n=136; see figure 2). Survival rates at 1, 3 and 5 years post-index were: 72% (95% CI 65.2% to 80.2%), 49% (95% CI 41.0% to 57.9%) and 35% (95% CI 28.2% to 44.4%), respectively. Of the 88 patients who died, cause of death was recorded for 45; of these, death was liver-related for 91% (n=41; liver decompensation (n=16, 39%), liver cancer (n=7, 17%), infection (n=4, 10%) and other causes (n=18, 44%)). Among patients with ARLD (n=95), survival rate at 1, 3 and 5 years post-index was 74% (95% CI 64.8% to 82.5%), 50% (95% CI 39.4% to 59.5%) and 36% (95% CI 26.1% to 45.4%).

### Treatment patterns

Of the 48 patients alive at 5 years, 33 were on RFX treatment at the end of the observation period. Of these 33 patients, 9 had discontinued and subsequently reinitiated RFX treatment, and 24 remained on treatment throughout the observation period. 114 patients discontinued RFX treatment during the observation period (66 between 1 and 5 years post-index). Of these, 105 patients discontinued permanently (48 due to death) and 9 subsequently reinitiated treatment. The most common reasons for discontinuation in living patients were liver transplantation (n=3), resolution of encephalopathy (n=6), clinical improvement

**Table 1** Demographic and clinical characteristics at initiation of RFX treatment

Demographic and clinical characteristics (n=138 unless specified otherwise)	
Female (n, %)	53 (38%)
Age, years (mean (±SD))	
At diagnosis of cirrhosis	58.2 (12.1)
At diagnosis of HE	60.2 (11.7)
At initiation of RFX	60.9 (11.6)
Phenotype (n, %)	
Overt	109 (79%)
Covert	29 (21%)
Time from cirrhosis diagnosis to initiation of RFX, months	
Mean (SD), n=133	32.3 (36.5)
Median (IQR), n=133	21.1 (6.7–47.2)
Time from HE diagnosis to initiation of RFX, months	
Mean (SD)	9.0 (17.6)
Median (IQR)	3.1 (0.4–10.5)
Underlying liver disease aetiology (not mutually exclusive, n (%))	
Alcohol-related liver disease	96 (70%)
Non-alcoholic steatohepatitis	32 (23%)
Hepatitis B or C	14 (10%)
Autoimmune hepatitis	2 (1%)
Non-alcoholic fatty liver disease	2 (1%)
Cryptogenic	4 (3%)
Other	3 (2%)
On liver transplant list at initiation (n, %)	
Yes	6 (4%)
No	132 (96%)
Proportion of patients with prior TIPSS at initiation of RFX (n, % n=131)	
Yes procedural	21 (16%)
No	110 (84%)
Not recorded	7
Child-Pugh score (n, % n=55)	
A	4 (7%)
B	32 (58%)
C	19 (35%)
Not recorded	83
MELD score (n, % n=100)	
<10	12 (12%)
10<15	37 (37%)
15<20	19 (19%)
20<25	11 (11%)
25 or higher	21 (21%)
Not recorded	38
ALBI score (n, % n=127)	
≤−2.60 (grade 1)	12 (9%)
>−2.60 to ≤−1.39 (grade 2)	63 (50%)
>−1.39 (grade 3)	52 (41%)
Not recorded	11
Alcohol use status (n, % n=117)	
Currently drinking alcohol	23 (20%)

Continued

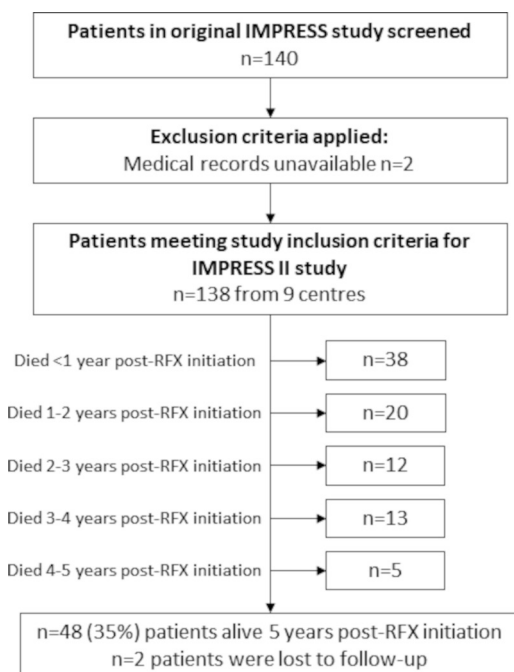
**Table 1** Continued

Demographic and clinical characteristics (n=138 unless specified otherwise)	
Not currently drinking alcohol	94 (80%)
Not recorded	21

ALBI, albumin-bilirubin; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RFX, rifaximin; TIPSS, transjugular intrahepatic portosystemic shunt.

(n=4) or being moved to end-of-life care (n=4; online supplemental table 3). In patients who were alive at 5 years post-index and did not undergo liver transplantation (n=37), the median time to RFX discontinuation was 0.8 (IQR 0.2–1.7) years. The median (IQR) time to RFX discontinuation in patients who discontinued due to HE resolution or clinical improvement (n=10) and in those who discontinued without HE resolution or clinical improvement (n=27) was 0.7 (IQR 0.3–1.3) and 0.8 (IQR 0.1–1.8) years, respectively. Use of concomitant laxatives is summarised in online supplemental table 4.

In patients who were alive at 2 years post-index (n=80), 93% reported no clinically relevant events, 4% reported variceal bleeding, 3% reported infections and 1% reported SBP between 1 and 2 years post-index. In patients who were alive at 5 years (n=50), 74% reported no clinically relevant events, 6% reported variceal bleeding, 14% reported infections, 4% reported SBP and 2% reported renal dysfunction/hepatorenal syndrome between 2 and 5 years post-index. The reported events were not mutually exclusive.

**Figure 1** Study flow (RFX denotes rifaximin- $\alpha$ ).

### Healthcare resource use

The total numbers of liver-related (all-cause) ED visits, inpatient admissions, ICU admissions and outpatient visits between 1 and 5 years post-index were 84 (156), 194 (310), 3 (6) and 709 (1123), respectively (online supplemental table 5). The median (IQR) lengths of stay for inpatient and ICU admissions from 1 to 5 years post-index for liver-related/all-cause HCRU were 4.0 (2.0–10.0)/3.0 (1.0–9.0) and 2.0 (1.5–3.5)/4.9 (2.0–5.0) days, respectively. Of all liver-related (all-cause) ED visits in the 1–5 years post-index, 66%–95% resulted in inpatient admissions, 0%–2% resulted in ICU admissions, and in 5%–33%, the patient was discharged home. For inpatient admissions in the 1–5 years post-index, between 93% and 95% resulted in the patient being discharged home, 0%–1% resulted in admission to ICU and 4%–7% resulted in deaths. Of the total 138 patients, 20% of patients recorded a subsequent liver-related admission and 30-day readmission within 1–5 years post-index. Of this 20%, 9% were before 2 years, 10% after 2 years and 1% recorded readmissions both before and after 2 years. The total number of readmissions was 76, with 41% of these between 1 and 2 years and 59% between 2 and 5 years. The 30-day liver-related readmission rate between year 1 and year 5 was 37% (76/206 admissions).

### DISCUSSION

This retrospective 5-year follow-up study aimed to provide evidence of long-term survival of patients with HE receiving RFX treatment. We have previously reported 12 months outcomes in this cohort.<sup>17</sup> The current results at 5 years post-initiation of RFX treatment show a survival rate of 35% and a 76% transplant-free survival rate. Additional findings suggest relatively low numbers of ED visits, inpatient and ICU admissions between 1 and 5 years post-initiation, suggesting a possible positive impact of RFX treatment on HCRU.

### Survival

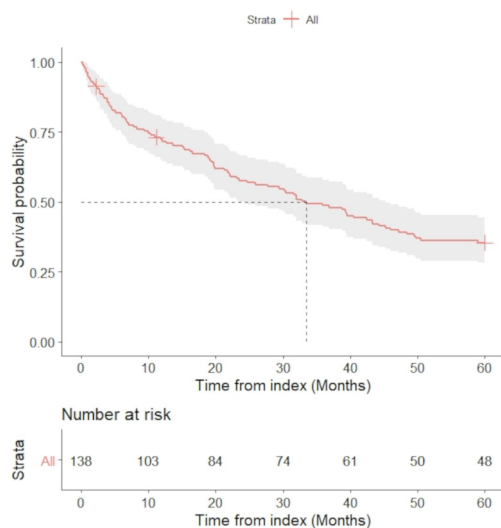
Survival was 72% at 1 year, in line with the original IMPRESS study (73%)<sup>13</sup> and higher than the 42%<sup>8</sup> and 44%<sup>10</sup> reported in patients with HE not receiving RFX treatment. It is also higher than the 1-year survival reported in HE cohorts where RFX treatment was mixed (48.3%)<sup>9</sup> or where RFX treatment status was not clarified (36%).<sup>1</sup> Importantly, RFX use was associated with reduced risk of death when included in a multivariable Cox model of survival in patients with HE.<sup>9</sup> The observed 5-year survival rate of 35% is also higher than the previously reported 5-year survival rate of patients with HE (15%).<sup>1</sup> Importantly, for comparison, the cohort studied by Jepsen *et al* had ARLD,<sup>1</sup> while the cohort here was mixed. The 36% survival rate in the comparable ARLD subgroup studied here lends weight to the suggestion that long-term RFX treatment may be associated with improved survival.

**Table 2** Liver-related clinical characteristics at 1, 2 and 5 years post-index

Characteristic	1 year	2 years	5 years
Liver transplant status	n (%=87)	n (%=67)	n (%=37)
Received transplant	3 (3%)	6 (9%)	9 (24%)
Not received transplant	84 (97%)	61 (91%)	28 (76%)
Not recorded	11	11	11
Not applicable*	38	58	88
Child-Pugh score	n (%=44)	n (%=18)	N (%=7)
A	15 (34%)	11 (61%)	4 (57%)
B	25 (57%)	6 (33%)	2 (29%)
C	4 (9%)	1 (6%)	1 (14%)
Not recorded	56	62	43
Not applicable*	38	58	88
MELD score	n (%=62)	n (%=16)	N (%=7)
<10	11 (18%)	7 (44%)	4 (57%)
10<15	27 (44%)	7 (44%)	2 (29%)
15<20	15 (24%)	2 (13%)	1 (14%)
20<25	3 (5%)	0 (0%)	0 (0%)
25 or higher	6 (10%)	0 (0%)	0 (0%)
Not recorded	38	64	43
Not applicable*	38	58	88
ALBI score	n (%=91)	n (%=65)	n (%=40)
≤-2.60 (grade 1)	9 (10%)	12 (18%)	12 (30%)
>-2.60 to ≤-1.39 (grade 2)	63 (69%)	41 (63%)	21 (53%)
>-1.39 (grade 3)	19 (21%)	12 (18%)	7 (18%)
Not recorded	10	15	10
Not applicable*	37	58	88
Alcohol use status	n (%=76)	n (%=38)	n (%=28)
Currently drinking alcohol	11 (14%)	5 (13%)	5 (18%)
Not currently drinking alcohol	65 (86%)	33 (87%)	23 (82%)
Not recorded	24	42	22
Not applicable*	38	58	88

\*Not applicable due to death.

ALBI, albumin-bilirubin; MELD, model for end-stage liver disease.



**Figure 2** Kaplan-Meier estimates of survival at 5 years post-rifaximin- $\alpha$  treatment. Crosshairs represent patients from whom data were censored.

The 1-year survival rate observed (72%) is lower than that previously reported at 2 years (81%).<sup>21</sup> Baseline MELD scores in the previous study had a maximum score of 24 (reflective of more restrictive inclusion/exclusion criteria), while in this real-world study, a fifth of patients had scores of 25 and above. Given higher MELD scores are associated with increased mortality, inclusion of these patients may account for the lower survival rate observed.<sup>22</sup> Additionally, both the observed 3-year and 5-year survival rates with RFX treatment (49% and 35%, respectively) are much higher than the 23% previously reported without RFX at 3 years, in line with the observation that RFX may be associated with increased survival.<sup>18 9</sup>

Although limited by low numbers of observations, prognostic scores (Child-Pugh, MELD and ALBI) appear to decrease in severity from index to year 2 (plateauing between 2 and 5 years). This may reflect deaths or liver transplantation in those with more severe liver disease, as was observed by Orr *et al* who

reported that patients with HE on RFX who died within 12 months follow-up had a significantly higher baseline MELD score than those who were alive at 1 year.<sup>16</sup> Alternatively, the data could indicate patients are improving on treatment or have stopped drinking alcohol. Further research is warranted to explore the long-term impact of RFX on prognostic scores.

It is unclear whether RFX directly improves survival in patients with HE, with conflicting results reported in two independent meta-analyses when compared with active treatments or placebo.<sup>14 23</sup> Other studies have suggested that RFX treatment may improve survival, but this remains to be substantiated by larger RCTs.<sup>24–27</sup>

### Treatment patterns

Discontinuation of therapy was common in those patients alive over 5 years (48%), with liver disease recovery with resolution of HE being the most common reason why treatment was stopped. Other studies report short-term discontinuation rates from 37% at 6 months to 10% at a year.<sup>15 16</sup> A high percentage of patients alive at 5 years (69%) remained on treatment, which is in line with previous findings of RFX being well tolerated in this patient group in both RCT and real-world settings up to 2 years,<sup>15 21</sup> and suggests that the long-term tolerability of RFX remains good up to 5 years.

### Healthcare resource use

Hospital outpatient visits were the most frequent type of healthcare contact in the 1–5 years post-index, with much lower numbers of ED visits and ICU admissions reported. The rate of cirrhosis complications reported is consistent with the clinical benefit of RFX treatment in HE that has been observed in previous studies.<sup>25 27</sup> Alternatively, the rates of complications could positively relate to the observed levels of alcohol abstinence (82%–87% between year 1 and year 5) in the ARLD cohort in which a low rate of complications might also be expected.<sup>28</sup> Published rates of 30-day readmission due to liver-related causes vary between 18% and 37% and thus the observed rate of 37% between 1 and 5 years is at the higher end of this range.<sup>7 29–31</sup> However, the cohorts for the majority of these studies captured the readmission rates of all patients with cirrhosis, while this study focused on those with HE (known to increase the likelihood of rehospitalisation). Taken together with previous observations of reduced HCRU post-RFX initiation,<sup>16 17</sup> the combined benefit of low recurrence of HE episodes, low number of complications and observed low rates of HCRU (outside of outpatient visits) support the rationale that RFX may provide a long-term economic benefit.<sup>14 31</sup>

### Strengths and limitations

The study was conducted in ‘real-world’ settings and recruited from a geographically diverse range of acute

centres including regional hospitals and transplant centres. The patient cohort displayed baseline demographics in line with the previous studies<sup>15–17</sup> and of UK patients with advanced liver disease,<sup>32</sup> suggesting they are broadly representative of the intended clinical population. The study is a retrospective design and is thus limited to routinely collected data recorded in medical records. Potential limitations of our study include that the reported results may be open to confounding effects and measures of HCRU did not include telemedicine or primary care. Additionally, while the inclusion of patients with covert HE in the study reflects real-world practice, it could potentially impact on the reported survival.

### Conclusions

This study provides real-world data from a geographically dispersed range of treatment centres on the long-term survival rates associated with RFX treatment in patients diagnosed with HE up to 5 years post-initiation. The favourable long-term outcomes, minimal HCRU and low rates of complications reported from this extension study further support the use of RFX in patients with HE.

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#### REFERENCES

- Jepsen P, Ott P, Andersen PK, *et al.* Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010;51:1675–82.
- Vilstrup H, Amodio P, Bajaj J, *et al.* Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. *Hepatology* 2014;60:715–35.
- Rahimi RS, Brown KA, Flamm SL, *et al.* Overt hepatic encephalopathy: current pharmacologic treatments and improving clinical outcomes. *Am J Med* 2021;134:1330–8.
- Bajaj JS, Schubert CM, Heuman DM, *et al.* Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology* 2010;138:2332–40.
- Romero-Gómez M, Córdoba J, Jover R, *et al.* Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. *Hepatology* 2007;45:879–85.
- Saab S. Evaluation of the impact of rehospitalization in the management of hepatic encephalopathy. *Int J Gen Med* 2015;8:165–73.
- Tapper EB, Halbert B, Mellinger J. Rates of and Reasons for Hospital Readmissions in Patients With Cirrhosis: A Multistate Population-based Cohort Study. *Clin Gastroenterol Hepatol* 2016;14:1181–8.
- Bustamante J, Rimola A, Ventura PJ, *et al.* Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol* 1999;30:890–5.
- Tapper EB, Aberasturi D, Zhao Z, *et al.* Outcomes after hepatic encephalopathy in population-based cohorts of patients with cirrhosis. *Aliment Pharmacol Ther* 2020;51:1397–405.
- Bohra A, Worland T, Hui S, *et al.* Prognostic significance of hepatic encephalopathy in patients with cirrhosis treated with current standards of care. *World J Gastroenterol* 2020;26:2221–31.
- National Institute for Health and Care Excellence. Rifaximin for preventing episodes of overt hepatic encephalopathy: NICE technology appraisal guidance [TA337], 2015. Available: <https://www.nice.org.uk/guidance/ta337> [Accessed 4 Nov 2021].
- Als-Nielsen B, Gluud LL, Gluud C. Non-Absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ* 2004;328:1046.
- Patel VC, Lee S, McPhail MJW, *et al.* Rifaximin- $\alpha$  reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. *J Hepatol* 2022;76:332–42.
- Han X, Luo Z, Wang W, *et al.* Efficacy and safety of rifaximin versus placebo or other active drugs in critical ill patients with hepatic encephalopathy. *Front Pharmacol* 2021;12:696065.
- Bass NM, Mullen KD, Sanyal A, *et al.* Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–81.
- Orr JG, Currie CJ, Berni E, *et al.* The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin- $\alpha$ . *Liver Int* 2016;36:1295–303.
- Hudson M, Radwan A, Di Maggio P, *et al.* The impact of rifaximin- $\alpha$  on the hospital resource use associated with the management of patients with hepatic encephalopathy: a retrospective observational study (IMPRESS). *Frontline Gastroenterol* 2017;8:243–51.
- Oey RC, Buck LEM, Erler NS, *et al.* The efficacy and safety of rifaximin- $\alpha$ : a 2-year observational study of overt hepatic encephalopathy. *Therap Adv Gastroenterol* 2019;12:1756284819858256.
- Salehi S, Tranah TH, Lim S, *et al.* Rifaximin reduces the incidence of spontaneous bacterial peritonitis, variceal bleeding and all-cause admissions in patients on the liver transplant waiting list. *Aliment Pharmacol Ther* 2019;50:435–41.
- Johnson PJ, Berhane S, Kagebayashi C, *et al.* Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol* 2015;33:550–8.
- Mullen KD, Sanyal AJ, Bass NM, *et al.* Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. *Clin Gastroenterol Hepatol* 2014;12:1390–7.
- Singal AK, Kamath PS. Model for end-stage liver disease. *J Clin Exp Hepatol* 2013;3:50–60.
- Kimer N, Krag A, Møller S, *et al.* Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther* 2014;40:123–32.

- 24 Kang SH, Lee YB, Lee J-H, *et al.* Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. *Aliment Pharmacol Ther* 2017;46:845–55.
- 25 Caraceni P, Vargas V, Solà E, *et al.* The use of rifaximin in patients with cirrhosis. *Hepatology* 2021;74:1660–73.
- 26 Lv X-Y, Ding H-G, Zheng J-F, *et al.* Rifaximin improves survival in cirrhotic patients with refractory ascites: a real-world study. *World J Gastroenterol* 2020;26:199–218.
- 27 Vlachogiannakos J, Viazis N, Vasiopoulou P, *et al.* Long-Term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol* 2013;28:450–5.
- 28 Pearson MM, Kim NJ, Berry K. Associations between alcohol use and Liver-Related outcomes in a large national cohort of patients with cirrhosis. *Hepatol Commun* 2020;2021:5.
- 29 Berman K, Tandra S, Forssell K, *et al.* Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. *Clin Gastroenterol Hepatol* 2011;9:254–9.
- 30 Volk ML, Tocco RS, Bazick J, *et al.* Hospital readmissions among patients with decompensated cirrhosis. *Am J Gastroenterol* 2012;107:247–52.
- 31 Roberts SB, Hansen BE, Shin S, *et al.* Internal medicine hospitalisations and liver disease: a comparative disease burden analysis of a multicentre cohort. *Aliment Pharmacol Ther* 2021;54:689–98.
- 32 National End of Life Care Intelligence Network, NHS The Health Research Authority. Deaths from liver disease: implications for end of life care in England, 2012. Available: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/governance-arrangement-research-ethics-committees/> [Accessed 8 Oct 2021].
- 33 Department of Health. Governance arrangements for research ethics committees: 2020 edition, 2020. Available: [https://www.hra.nhs.uk/media/documents/GAfREC\\_Final\\_v2.0\\_26.03.2020.pdf](https://www.hra.nhs.uk/media/documents/GAfREC_Final_v2.0_26.03.2020.pdf) [Accessed 13 Feb 2019].