Hepatic Encephalopathy Update: Reports From ACG 2012 and The Liver Meeting 2012

Overt hepatic encephalopathy (OHE), along with ascites and esophageal and gastric varices, is a primary complication of cirrhosis of the liver. An estimated 5.5 million people in the United States have hepatic cirrhosis and, of these, 30% to 45% will develop OHE. The burden of cirrhosis is increasing in the United States. Hospital discharges due to cirrhosis (all listed diagnoses) increased by 6% from 2009 (498,181 patients) to 2010 (526,096 patients). While it is difficult to estimate the true incidence of OHE, it appears to be increasing at an even higher rate than cirrhosis. During the same time period, hospital discharges for hepatic encephalopathy (all listed diagnoses) increased by 21% from 2009 (345,887 patients) to 2010 (419,389 patients).

The development of OHE in those with cirrhosis is an unfavorable sign. Without appropriate prophylactic therapy to prevent recurrence and/or the patient having had a liver transplant, the survival probability is 42% at 1 year and 23% at 3 years. The first step in managing the acute stage of OHE involves identifying and treating the precipitating cause. Precipitating causes include hypovolemia, gastrointestinal bleeding, infection, dehydration secondary to diuretic use, diarrhea, vomiting, hyponatremia, hypokalemia or hyperkalemia, alkalosis, surgery, renal failure, transjugular intrahepatic portosystemic shunt, constipation, benzodiazepine use, narcotic use, hypoxemia, hepatoma, and noncompliance with lactulose therapy.

Simultaneously with identification and correction of the precipitating cause, therapy aimed at reducing the nitrogenous load in the intestine to reduce the accumulation of ammonia is instituted. Ammonia is thought to play a major role in the pathogenesis of hepatic encephalopathy. The cirrhotic liver is unable to metabolize ammonia formed when protein is broken down by bacteria in the intestines, resulting in an increase in serum ammonia. Uptake of ammonia by astrocytes causes cerebral edema and resultant neurologic dysfunction. The two primary therapies currently used to reduce circulating ammonia are the nonabsorbable disaccharide, lactulose, and the nonabsorbable antibiotic, rifaximin. Either agent can be used during the acute stages of OHE and lactulose, rifaximin, or combination lactulose/rifaximin should be used prophylactically following recovery from OHE to prevent recurrence. Prophylactic therapy, referred to as secondary prophylactic when instituted to prevent recurrence of OHE following an OHE episode, should continue for an indefinite period or until liver transplantation.

The studies presented have not been validated by peer reviewers, but are platform presentations, posters, etc presented at a scientific meeting. Use caution in drawing conclusions until published in peer-reviewed journals.

Objectives:
After reading and studying this newsletter, the participant should be able to:

- Assess emerging new therapies for the treatment of acute overt hepatic encephalopathy and as secondary prophylactic agents for the prevention of recurrence of overt hepatic encephalopathy
- Evaluate long-term rifaximin efficacy and safety data as secondary prophylactic therapy for overt hepatic encephalopathy
- Describe survival probability of patients who have experienced overt hepatic encephalopathy and how choice of secondary prophylactic treatment may affect survival probability
Polyethylene glycol 3350-electrolyte solution (PEG) vs. lactulose for patients hospitalized with acute OHE

Lactulose has been used to reduce serum ammonia concentrations in patients with OHE. Lactulose acidifies the fecal stream, causing protonation of ammonia (NH$_3$) into ammonium ions (NH$_4^+$). Absorption of the charged NH$_4^+$ ions is limited, causing NH$_4^+$ to remain trapped in the colonic lumen. The cathartic action of lactulose can also enhance elimination of ammonia.4 Animal studies suggested that polyethylene glycol 3350-electrolyte solution (PEG; Golytely®) may be effective at clearing intestinal bacteria and reducing bacterial ammoniagenesis. Rahimi et al compared the effects of lactulose (n=25) and PEG (n=25) in hospitalized patients with acute OHE.5 Patient demographics, clinical characteristics, and laboratory values were similar in both arms of the study. Severity of OHE was assessed using the hepatic encephalopathy scoring algorithm (HESA), which combines clinical impressions with neuropsychological performances to characterize OHE. Study results are summarized in Table 1.

Table 1. Effect of lactulose vs. PEG treatment on 24-hour hepatic encephalopathy scoring algorithm (HESA), overall response, and length of hospitalization in patients with acute OHE.6

<table>
<thead>
<tr>
<th></th>
<th>Lactulose (mean ± SD)</th>
<th>PEG (mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HESA</td>
<td>2.3 ± 0.8</td>
<td>2.3 ± 0.9</td>
<td>0.787</td>
</tr>
<tr>
<td>24 hour HESA</td>
<td>1.8 ± 0.9</td>
<td>0.9 ± 1</td>
<td>0.015</td>
</tr>
<tr>
<td>Overall response within 24 hours (%)</td>
<td>52</td>
<td>91</td>
<td>0.002</td>
</tr>
<tr>
<td>Length of stay</td>
<td>7.8 ± 12</td>
<td>3.7 ± 3.5</td>
<td>0.110</td>
</tr>
</tbody>
</table>

The percentage of patients receiving PGB with at least one OHE episode was significantly reduced compared to placebo (21% PGB vs. 36% placebo). Patients receiving PGB, compared to placebo, also had significant reductions in total OHE events (35 PGB vs. 57 placebo), days with CHESS score ≥3 (13 PGB vs. 27 placebo), and time normalized NH$_3$ AUC (46 PGB vs. 58 placebo). Changes in total OHE hospitalizations and total OHE hospitalization days, although reduced in the PGB group compared to the placebo group, were not statistically significant. The percentages of patients reporting adverse events were similar in the PGB (79%) and placebo (76%) study arms. Interestingly, PGB had a strong treatment effect in patients who were not on rifaximin at baseline, but had little effect in those who were receiving rifaximin at baseline. The authors concluded that PGB shows promise as a secondary prophylactic agent for the prevention of recurrent OHE with a strong treatment effect in non-rifaximin patients and the potential for incremental benefit in rifaximin patients.

A probiotic preparation for secondary prophylaxis of OHE in cirrhotic patients

A recent Cochrane Database System review of clinical studies that used probiotics for the treatment of OHE questioned their efficacy in altering clinically relevant outcomes.10 Dhiman et al conducted a study to ‘demonstrate the unequivocal efficacy of a probiotic preparation for the prevention of OHE recurrence, the reduction in hospitalizations, and for improving the severity of liver disease in cirrhotic patients.11 The randomized, double-blind, placebo-controlled trial involved patients with liver cirrhosis who recovered from an OHE episode during the previous 1 month. Patients received either a probiotic preparation (VSL#3, which contained Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, streptococcus faecalis, and lactobacillus acidophilus) or placebo (vitamin/mineral complex) for 6 months. The primary endpoints were the proportion of patients with ≥1 OHE episode during the study period and the number of OHE hospitalizations and total OHE hospitalization days. The authors concluded that the probiotic preparation significantly reduced the proportion of patients with ≥1 OHE episode during the study period compared to placebo (21% probiotic vs. 36% placebo). Patients receiving the probiotic preparation also had significant reductions in total OHE events, days with CHESS score ≥3, and time normalized NH$_3$ AUC compared to placebo.

Table 2. Effects of probiotics on OHE hospitalizations and total OHE hospitalization days.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=59)</th>
<th>Rifaximin naïve (n=19)</th>
<th>Rifaximin at Baseline (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHE hospitalizations</td>
<td>35 ± 134 (n=60)</td>
<td>13 ± 58 (n=59)</td>
<td>66 ± 134 (n=59)</td>
</tr>
<tr>
<td>Days with CHESS score ≥3</td>
<td>13 ± 0.044 (n=59)</td>
<td>12 ± 0.056 (n=59)</td>
<td>16 ± 0.071 (n=59)</td>
</tr>
<tr>
<td>OHE hospitalization days</td>
<td>66 ± 36 (n=59)</td>
<td>46 ± 13 (n=59)</td>
<td>86 ± 22 (n=59)</td>
</tr>
<tr>
<td>Subjects reporting AEs</td>
<td>79% (n=47)</td>
<td>79% (n=15)</td>
<td>80% (n=32)</td>
</tr>
</tbody>
</table>

The study results are summarized in Table 2.

The material was supported by an educational grant from Salix Pharmaceuticals, Inc.
Bifidobacterium infantis, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillli bulgaricus) or placebo for 6 months. VSL#3 was administered at a dose of 900 billion bacteria daily to 51 patients; 52 patients received placebo. The study results are presented in Table 3.

Table 3. Effects of administration of VSL#3 probiotic for 6 months vs. placebo in patients who have recovered from an episode of OHE during previous 1 month.\(^{11}\)

While fewer patients treated with probiotic (25.5%) had breakthrough OHE compared to placebo (36.5%), the difference was not statistically significant. Overall hospitalizations for probiotic vs. placebo (19.6% vs. 42.3%) and OHE-related hospitalizations for probiotic vs. placebo (15.7% vs. 34.6%) were significantly different. When comparing 6-month values with baseline values, significant improvements were seen in the Child-Turcotte-Pugh score (8.7 → 7.2) and in serum interleukin-6 levels (60.3 pg/mL → 33.4 pg/mL) in patients receiving probiotic; changes in the Child-Turcotte-Pugh score and in serum interleukin-6 concentrations were not statistically significant in patients receiving placebo. The authors concluded that secondary prophylactic treatment with the probiotic VSL#3 of patients who had recovered from an OHE episode significantly reduced the risk of overall hospitalizations including those involving OHE and also significantly reduced Child-Turcotte-Pugh scores and serum interleukin-6 concentrations. While breakthrough OHE was reduced, the change was not statistically significant.

**Long-term use of rifaximin as secondary prophylaxis for the prevention of recurrence of OHE**

In a 6-month study, rifaximin prophylactic therapy reduced the risk of OHE recurrence in cirrhotic patients with a history of OHE by 58% compared to placebo. OHE-related hospitalizations were also reduced.\(^{12}\) Since secondary prophylactic therapy should be continued indefinitely or until liver transplant, a long-term, open-label extension study was conducted to examine the long-term efficacy and safety of rifaximin. Bajaj et al reported on the long-term outcomes of a subset of patients (n=51) who were in the placebo arm of the 6-month study and who crossed over to rifaximin (550 mg twice daily) in the open-label extension study.\(^{12}\) The total person-years of exposure was 134.2. Maintenance of remission was maintained for up to 840 days in some patients. The OHE breakthrough event rate and OHE-related hospitalization event rate were significantly lower after crossover than the corresponding event rates during prior placebo treatment (P<0.0001 and P<0.01, respectively; Figure 1). The rates of the most common treatment-emergent adverse events in placebo crossover patients were similar to those observed in the placebo arm of the 6-month study (Table 4). Similarly, rates of infection in the placebo crossover patients were comparable to rates observed in the 6-month study with the exception of pneumonia, which was not seen in placebo patients during the 6-month trial (Table 4). The authors concluded that rifaximin therapy for up to 840 days in cirrhotic patients who had received placebo in the 6-month study reduced the risk of OHE recurrence and OHE-related hospitalizations without increasing the rates of adverse events or infections.

### Table 4. Incidence and rate of most common treatment-emergent adverse events in patients treated with placebo for 6 months compared to the incidences and rates in the same patients following crossover to rifaximin for up to 840 days.\(^{13}\)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n=82)</th>
<th>Crossover to Rifaximin (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>9 (0.36)</td>
<td>18 (0.16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (0.47)</td>
<td>17 (0.14)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (0.33)</td>
<td>7 (0.06)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (0.32)</td>
<td>8 (0.06)</td>
</tr>
</tbody>
</table>

### Incidence and rate of infections

- **Cellulitis**: 2 (0.08) vs. 11 (0.09)
- **Intestinal infections**: 0 (0) vs. 1 (0.007)
- **Peritonitis**: 3 (0.11) vs. 5 (0.04)
- **Pneumonia**: 0 (0) vs. 10 (0.08)
- **Septicemia/septic shock**: 2 (0.08) vs. 10 (0.08)
- **Urinary tract/kidney infection**: 7 (0.28) vs. 14 (0.12)

*Note: rates calculated as number of patients with particular adverse event / total person-years of exposure.*

*PYE = total person-years of exposure.

*TEAE = treatment-emergent adverse events occurring in ≥10% of patients in placebo arm of 6-month trial.
Long-term survival following overt hepatic encephalopathy

Long-term survival data for patients with OHE is rather limited. A retrospective study by Neff et al provides updated survival data not only for those who received no secondary prophylactic therapy, but also differentiates post-OHE survival in those who received secondary prophylactic therapy according to the agent(s) utilized. Medical charts of patients admitted to a large transplant program between December 2000 and May 2012 were examined. Four groups were identified including patients receiving lactulose monotherapy (n=58), patients receiving lactulose combined with rifaximin (n=55), patients receiving rifaximin monotherapy (n=28), and patients receiving no secondary prophylactic therapy (n=44). Data collected included post-discharge HE management protocol and time to transplant or death.

The results are illustrated graphically in Figure 2. At each time point, survival with rifaximin monotherapy > survival with lactulose/rifaximin combination therapy > survival with lactulose monotherapy > survival with no secondary prophylactic therapy for recurrent OHE. Survival differences between the lactulose group and the rifaximin group were significant (P=0.049). The authors concluded that rifaximin, either as monotherapy or in combination with lactulose, improves both short- and long-term survival compared to lactulose monotherapy or no therapy when used as secondary prophylaxis for recurrent OHE.

Secondary prophylactic treatment patterns in patients following an episode of OHE

Practice guidelines for the treatment of OHE have never been issued by the American Association for the Study of Liver Diseases or the American Gastroenterological Association, and the guidelines issued by the American College of Gastroenterology (ACG) published in 2001 are outdated. While the ACG guidelines list ‘Assessment of the Need for Long Term Therapy’ as a treatment goal, no specific recommendations are provided. Experts in the field, however, recommend treatment with lactulose monotherapy, rifaximin monotherapy, or lactulose/rifaximin combination therapy as secondary prophylactic therapy following recovery from the acute stages of OHE. Secondary prophylactic therapy should be continued for an indefinite period of time or until liver transplantation.

A retrospective review of a subset of national claims for medical and hospital activity from January 2009 to December 2011 suggests, however, that most OHE patients are not currently receiving secondary prophylactic therapy. In the review, patient selection was based on claims with an ICD-9 code 572.2 (HE). Claims from eligible patients were reviewed for any filled prescriptions for rifaximin, lactulose, or rifaximin/lactulose combination therapy. A total of 13,623; 15,529; and 16,328 patients were identified for 2009, 2010, and 2011, respectively. Treatment patterns observed are summarized in Table 5. Surprisingly, the percentage of OHE patients receiving either inpatient therapy with lactulose, rifaximin, or rifaximin/lactulose actually decreased over the 2009 to 2011 sample interval from 89.2% to 86.4%. The percentage of patients receiving secondary prophylactic therapy after hospital discharge following an OHE episode also decreased over the sample interval from 39.7% to 36.1%. Another finding in the OHE treatment study was that the approval of rifaximin for the treatment of recurrence of OHE in 2010 changed the choice of therapy for OHE from 2009 to 2011, with a reduction in the percentage of patients receiving lactulose monotherapy (27.9% → 14.1%) and an increase in the percentages receiving either rifaximin monotherapy (3.9% → 13.2%) or rifaximin/lactulose combination therapy (8.1% → 8.8%). The authors were unable to identify the cause of the low treatment rates, but suggested the reason may be a failure of patients to fill prescriptions (lack of insurance, other financial concerns, and/or noncompliance) and/or healthcare providers not being adequately educated about the benefits of treatment.

<table>
<thead>
<tr>
<th>Eligible patients identified (n)</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with inpatient claims (%)</td>
<td>89.2%</td>
<td>87.8%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Patients receiving ongoing treatment (%)</td>
<td>39.7%</td>
<td>37.7%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>

Table 5. Review of a subset of filled prescription claims (rifaximin, lactulose, and rifaximin/lactulose combination therapy) for patients with an ICD-9 code 572.2 (HE) while they were hospitalized and following recovery.

Summary

The burden of hepatic cirrhosis and OHE in the United States is increasing. Promising advances in the treatment of OHE are taking place as indicated in this review of selected presentations from ACG 2012 and The Liver Meeting 2012. Polyethylene glycol 3350-electrolyte solution (Golytely®) may emerge as an alternative to lactulose in the treatment of acute episodes of OHE. Glycerol phenylbutyrate, which enhances urinary excretion of a metabolite of urea, thus lowering serum concentrations of urea, significantly decreased OHE episodes when compared to placebo; changes in OHE hospitalizations and total hospitalization days, although fewer in number compared to placebo, were not statistically significant. In contrast, treatment with the probiotic VSL#3 produced significant reductions in OHE hospitalizations and total hospitalization days when compared to placebo, but the effect of VSL#3 on breakthrough OHE compared to placebo was not significant. Long-term administration of rifaximin (up to 840 days) in patients who had received placebo in a 6-month study prior to crossover significantly reduced the risk of OHE recurrence and OHE-related hospitalization without increasing the...
rates of adverse events or infections. Although experts recommend continuation of secondary prophylactic therapy with lactulose, rifaximin, or lactulose/rifaximin therapy for an indefinite period of time or until liver transplantation, a retrospective review of patient records suggests that only one-third of patients actually receive long-term prophylaxis following recovery from an OHE episode.
References


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Required with 70% passing.

1. Which of the following agents lowers serum ammonia through metabolism to a urea surrogate that is excreted in the urine?
   a. Rifaximin
   b. Lactulose
   c. Polyethylene glycol 3350-electrolyte solution
   d. Glycerol phenylbutyrate

2. In the study by Dhiman et al, the probiotic VSL#3 was statistically significantly better in all of the following except:
   a. Breakthrough overt hepatic encephalopathy compared to placebo
   b. Overall hospitalizations compared to placebo
   c. Overt hepatic encephalopathy-related hospitalizations compared to placebo
   d. Improvement in Child-Turcotte-Pugh score at 6 months compared to baseline

3. When compared to rates observed during a 6-month study in which they received placebo, patients who were crossed over to rifaximin in a long-term extension study:
   a. Had an increase in the rates for the most common treatment-emergent adverse events
   b. Had a decrease in the rates for cellulitis, intestinal infections, pneumonia, and sepsis/septic shock
   c. Had a decrease in the rate of overt hepatic encephalopathy breakthrough events
   d. Had an increase in the rate of overt hepatic encephalopathy-related hospitalizations

4. A retrospective study of long-term survival for patients following recovery from overt hepatic encephalopathy found that survival was longest in patients receiving which secondary prophylactic agent(s)?
   a. Lactulose monotherapy
   b. Rifaximin monotherapy
   c. Lactulose/rifaximin combination therapy
   d. Probiotic monotherapy

5. A retrospective review of claim data found that the percentage of patients that actually received secondary prophylactic therapy for overt hepatic encephalopathy in 2011 was:
   a. <16%
   b. 36%
   c. 56%
   d. >76%
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- Patient care or patient-centered care
- Practice-based learning and improvement
- Interpersonal and communication skills
- Employ evidence-based practice
- Interdisciplinary teams
- Professionalism
- Quality improvement
- Medical knowledge
- System-based practice
- Utilize informatics
- None of the above

• The content of this activity matched my current (or potential) scope of practice.

- No
- Yes, please explain

• Was this activity scientifically sound and free of commercial bias* or influence?

- Yes
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* Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.
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  - I will not make any changes to my practice
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• What new information did you learn during this activity?
  __________________________________________________
  __________________________________________________

• Please indicate any barriers you perceive in implementing these changes.
  - Lack of experience
  - Lack of resources (equipment)
  - Lack of time to assess/counsel patients
  - Lack of consensus of professional guidelines
  - Lack of opportunity (patients)
  - Lack of administrative support
  - Reimbursement/insurance issues
  - Patient compliance issues
  - No barriers
  - Cost
  - Other ______________________________

• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients’ outcomes?
  __________________________________________________
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• Comments to help improve this activity?
  __________________________________________________
  __________________________________________________

• Recommendations for future CME/CPE topics.
  __________________________________________________
  __________________________________________________

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First Name: __________________________________________________________________________

Middle Initial: ________________________________________________________________________

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City: __________________________________________________________________________________

State or Province: _____________________________________________________________________

Postal Code: __________________________________________________________________________

Phone: __________-________-__________ Ext.: __________

Fax: __________-________-__________

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