HEPATOLOGY NEWS TONIGHT
MANAGING COMPLICATION OF CIRRHOSIS

TUESDAY, APRIL 10, 2018
ORLANDO WORLD CENTER MARRIOTT

SUPPORTED BY AN EDUCATIONAL GRANT FROM SALIX PHARMACEUTICALS.
HELD IN CONJUNCTION WITH HOSPITAL MEDICINE 2018, SHM'S ANNUAL CONFERENCE.
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Educational Objectives

• Understand the complications and the consequences of chronic liver disease
• Describe the economic, patient and caregiver burdens associated with cirrhosis and HE
• Demonstrate the ability to properly treat HE patients and prevent recurrence of disease
Cirrhosis Is The Final Pathway for Most Chronic Liver Diseases

Decompensation/ liver failure

Hepatocellular carcinoma

Liver transplantation

Accumulation of collagen deposition = fibrosis → cirrhosis

Prevalence of Cirrhosis

0.27% Estimated prevalence of cirrhosis in US

633,323 Estimated number of Americans with cirrhosis

69% Patients with cirrhosis are unaware of their disease

Compensated cirrhosis often undetected for long periods of time

Global prevalence of cirrhosis is unknown

Compensated Cirrhosis May Be Difficult To Recognize

- Most patients remain asymptomatic until decompensation occurs\(^1\)
- Subtle clues may be overlooked
  - Thrombocytopenia
  - Muscle wasting
  - AST>ALT without alcohol consumption
  - Liver enzymes may not be abnormal
- Etiology may be remote
  - Prior alcohol use
  - Uncontrolled diabetes mellitus and obesity

Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Stage Over Time

2 year median survival once decompensation occurs

Survival Is Significantly Longer in Compensated Cirrhosis Compared with Decompensated Cirrhosis

Survival According to Decompensation At Diagnosis

>12 year median survival in patients with compensated cirrhosis

Complications of Cirrhosis: Distinguish Portal Hypertension from Liver Insufficiency

- Portal hypertension
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
  - Variceal hemorrhage
  - Ascites
  - Hydrothorax
  - Spontaneous bacterial peritonitis
    - Hepatorenal syndrome

- Liver insufficiency
  - Encephalopathy
    - 30-40% of cirrhotic patients
    - “Coagulopathy”
      - Jaundice
      - Hypoalbuminemia

Patient Case

HISTORY & PE

HPI
• History of NASH and noted cirrhosis based on abdominal US about 2 years ago
• Noted melena for 2 days
• His spouse noted that he has become confused in the last few days and became unresponsive on the day of admission

Social History
• Used to drink heavily as a longshore man when he was young
• Quit drinking and smoking for the last 10 years
• Lives with wife in a condo
• Wife has breast cancer and is undergoing chemotherapy

73-yr-old man admitted for OHE for the first time
73-yr-old man admitted for OHE for the first time

- Confused, disoriented
- Anemic, but not icteric
- Positive flapping, tremor
- No ascites, not tender
- Trace edema
- Stool tarry and Hemoccult (+)

**BP** 110/60 mm Hg
**PR** 110/min
**RR** 20/min
**BMI** 35 kg/m²
Patient Case (cont.)

73-yr-old man admitted for OHE for the first time

MEDICATIONS

Lisinopril
Metformin
Simvastatin
Baby aspirin
<table>
<thead>
<tr>
<th>LABS</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/H</td>
<td>9.8/31</td>
</tr>
<tr>
<td>Platelets</td>
<td>90,000</td>
</tr>
<tr>
<td>INR</td>
<td>1.6</td>
</tr>
<tr>
<td>Ammonia level</td>
<td>120</td>
</tr>
<tr>
<td>BUN</td>
<td>30</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5</td>
</tr>
<tr>
<td>Na</td>
<td>134</td>
</tr>
<tr>
<td>K</td>
<td>3.2</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>50/32</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.0</td>
</tr>
<tr>
<td>Alk phos</td>
<td>120</td>
</tr>
</tbody>
</table>
Definition of Hepatic Encephalopathy

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and portal systemic shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.
Glutamate and NH$_2$

Glutamine

Inflammation

Proinflammatory cytokines

Nitric oxide and oxidative stress

Astrocyte swelling

NH$_3$

Cerebral blood flow

ICP, intracranial pressure.
Portal-Systemic Shunting Contributes to HE Pathogenesis

Patient Case

How do you classify this patient’s HE?

What is the role of ammonia testing?
Characterization of HE Stages

Categorization is often arbitrary and varies between raters

“Overt” HE Stages

Clinical Diagnosis

Worsening cognitive dysfunction

# Clinical Classification of HE

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Time course</th>
<th>Spontaneous or precipitated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MHE</td>
<td>Covert</td>
<td>Spontaneous</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>Recurrent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>Precipitated (specify)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>Persistent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

Precipitating Factors For HE

Increased ammonia production
- GI hemorrhage
- Excessive dietary protein
- Blood transfusion
- Electrolyte imbalance (eg, hypokalemia)
- Constipation

Portosystemic shunts
- Spontaneous
- Iatrogenic (eg, TIPS)

Other
- Drugs (eg, opioids, benzodiazepines)
- Infections (eg, SBP)
- Malignancy (eg, hepatoma)

“Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”

Except in acute liver failure, ammonia level >200 μmol/L is predictive of poor outcome.

Patient Case

How do you manage this patient?
AASLD Recommends 4-Pronged Approach to Treating OHE*

1. Initiate care for patients with altered consciousness
2. Seek and treat alternate causes of altered mental status
3. Identify and correct precipitating factors
4. Begin empirical HE treatment

*Grade II-2, A, 1 recommendation.
US Hospital Discharges Due to Cirrhosis Are Increasing

<table>
<thead>
<tr>
<th>Year</th>
<th>Discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>403,665</td>
</tr>
<tr>
<td>2005</td>
<td>411,029</td>
</tr>
<tr>
<td>2006</td>
<td>436,901</td>
</tr>
<tr>
<td>2007</td>
<td>444,883</td>
</tr>
<tr>
<td>2008</td>
<td>459,496</td>
</tr>
<tr>
<td>2009</td>
<td>498,181</td>
</tr>
<tr>
<td>2010</td>
<td>526,096</td>
</tr>
<tr>
<td>2011</td>
<td>576,573</td>
</tr>
</tbody>
</table>

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.
Health Care Resource Utilization in Patients Discharged with HE Diagnosis

Average hospitalization charges

Number of procedures

Average charge, 2009 USD

Average hospitalization charges

Number of procedures

P<0.001

P<0.001

Treatment Goals for Overt HE

- Provision for supportive care
- Identification and removal of precipitating factors
  - Infection, GI bleed, dehydration
- Reduction of nitrogenous load from gut
- Correction of electrolyte abnormalities
- Long-term therapy assessment
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of need for liver transplantation

## Current Therapy Options for HE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose¹</td>
<td>Poorly absorbed disaccharide</td>
<td>• Decrease blood ammonia concentration&lt;br&gt;• Prevention and treatment of portal-systemic encephalopathy</td>
</tr>
<tr>
<td>Rifaximin²</td>
<td>Non-aminoglycoside semi-synthetic, nonsystemic antibiotic</td>
<td>Reduction in risk of OHE recurrence in patients ≥18 years of age</td>
</tr>
<tr>
<td>Neomycin³</td>
<td>Aminoglycoside antibiotic</td>
<td>Not to be used, renal and ototoxic risk</td>
</tr>
<tr>
<td>Metronidazole¹</td>
<td>Synthetic antiprotozoal and antibacterial agent</td>
<td>Not approved for HE</td>
</tr>
<tr>
<td>Vancomycin¹</td>
<td>Aminoglycoside antibiotic</td>
<td>Not approved for HE</td>
</tr>
</tbody>
</table>

Lactulose for HE

• Current mainstay of HE therapy\(^1,^2\)

• Mechanism of action\(^2-^5\)
  – Non-absorbable disaccharide is fermented in the colon and metabolized by bacterial flora to lactic acid, lowering colonic pH
  – Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume

Non-absorbable disaccharides were associated with beneficial effects on HE, mortality, and serious adverse events.
Practical Considerations for Use of Lactulose in HE

Dosage/Administration
- Administered orally, by mouth or through a nasogastric tube or via retention enemas\(^1,2\)
- Initiated at 25 mL every 1-2 hours to achieve ≥2 soft of loose stools per day\(^2\)

Safety
Key side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence\(^1,3\)

Rifaximin

Description

• Minimally absorbed (<0.4%) oral antibiotic\textsuperscript{1,2}
• Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria\textsuperscript{2}

Indication

• 550 mg BID for reduction in risk of OHE in patients \geq 18\text{ years of age}\textsuperscript{2}

Safety

• No clinical drug interactions reported\textsuperscript{2}
• No dosing adjustment required in patients with liver disease or renal insufficiency\textsuperscript{2}

Rifaximin Randomized, Controlled Trial:
Time to First Breakthrough HE Episode Primary Endpoint

Proportion of Patients Without Breakthrough HE (%)

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)


*Rifaximin 550 mg or placebo twice daily. 91% of patients in both arms received concomitant lactulose.
Frequency and Duration of Hospitalization Associated with Lactulose and Rifaximin in HE

Mean Number of Hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>Mean number of hospitalizations</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Mean Days per Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Mean days per hospitalization</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

*P <0.001 rifaximin period versus lactulose period, paired t-test
Hospitalization Duration and Charges Associated with Lactulose and Rifaximin in HE

1.8  
0.4  

Mean total weeks of hospitalization

0 0.5 1 1.5 2

Lactulose  
Rifaximin

n=145  n=141

P<0.001

Mean days per hospitalization

0 10,000 20,000 30,000 40,000 50,000 60,000

Lactulose  
Rifaximin

n=141  n=138

P<0.001

Mean total weeks of hospitalization

0 0.5 1 1.5 2

Lactulose  
Rifaximin

n=145  n=141

P<0.001

Mean days per hospitalization

0 10,000 20,000 30,000 40,000 50,000 60,000

Lactulose  
Rifaximin

n=141  n=138

P<0.001

*Charges were calculated in 2005 dollars based on average cost per hospital day as determined by the 2003 Healthcare Cost Utilization Project for ICD-9-CM principal diagnosis code 572.2. A healthcare cost index was used to predict 2004 and 2005 costs. Leevy CB, Phillips JA. Dig Dis Sci. 2007;52:737-741.
Hospital Course

- He has EGD with variceal banding and bleeding stopped
- Mental status improved with lactulose but dosage has to be reduced due to significant diarrhea and rifaximin was added 3 days before discharge
  - His wife was instructed to follow up in one week after discharge
What is the social burden of HE?
HE Impacts Family Daily Functioning

Impact of Cirrhosis-Related Expenses on Daily Activities of Affected Families Within Past 3 Years

- Stopped saving: 56%
- In debt: 46%
- No education: 16%
- Late on bills: 15%
- No food: 11%
- Moved out: 10%
- Bankrupt: 7%
- Evicted: 5%

Caregiver Burden Increases with HE Severity

Mean (±SE) Caregiver Scores in the Objective Burden Domain of the Caregiver Burden Inventory

Hospital Course

- He was re-admitted 10 days later due to recurrent grade III encephalopathy without melena
- He is taking lactulose only but unable to obtain rifaximin after discharge
  - He has not seen his PCP yet
Impact of Affordable Care Act on Patients with HE

- Under the ACA, CMS assigns penalties to hospitals for underperformance in certain conditions
- CMS has selected certain core conditions to measure and evaluate
- Measures
  - 30-day readmission rates
  - Average length of stay
  - Mortality
- While the ACA does not currently include regulations for HE, in a retrospective review of 21 million inpatient admissions in 2014, 42% of patients admitted with HE presented with a core measure comorbidity

<table>
<thead>
<tr>
<th>Care Measure Conditions</th>
<th>Hospital-Acquired Conditions</th>
</tr>
</thead>
</table>
| Acute myocardial infarction (AMI) | • Central-line associated blood stream infection (CLA-BSI)  
• Methicillin-resistant *staphylococcus aureus* (MRSA) |
| Heart failure (HF) | • Catheter-associated urinary tract infection (CA-UAT)  
• *Clostridium difficile* |
| Chronic obstructive pulmonary disorder (COPD) | • Sepsis  
• Falls |
| Pneumonia | • Pressure ulcers |

ACA, Affordable Care Act; CMS, Centers for Medicare & Medicaid Services.  
Data on File, Salix Pharmaceuticals, 2014.
Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common

- Retrospective study of 402 patients from an academic transplant center
  - Follow-up time censored at death, elective admissions such as transplant or post-procedure observation, or the date of last clinic note; median follow-up was 203 days
  - Included cirrhotic patients hospitalized for ascites, SBP, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to readmission was 67 days
- Median number of readmissions was 2 (range 0-40); overall rate was 3 hospitalizations/person-year

All-Cause and HE-Related Re-Hospitalization for Patients with Hepatic Encephalopathy

### Unadjusted and Adjusted Odds Ratios for 30-Day Readmissions by Condition for Complications of Liver Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unadjusted OR (95% CI)</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>1.28 (1.20-1.37)</td>
<td>1.47 (1.37-1.58)</td>
<td>1.78 (1.66-1.90)</td>
</tr>
<tr>
<td>Variceal hemorrhage</td>
<td>1.85 (1.71-2.00)</td>
<td>1.69 (1.56-1.83)</td>
<td>1.55 (1.43-1.69)</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td><strong>2.62 (2.41-2.83)</strong></td>
<td><strong>2.67 (2.46-2.89)</strong></td>
<td><strong>3.23 (2.97-3.52)</strong></td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>2.33 (1.90-2.85)</td>
<td>2.46 (2.00-3.02)</td>
<td>1.41 (1.13-1.77)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1.79 (1.61-2.00)</td>
<td>1.64 (1.45-1.84)</td>
<td>1.70 (1.51-1.91)</td>
</tr>
</tbody>
</table>
### 90-Day Hepatology Readmission

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unadjusted OR (95% CI)</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>1.11 (1.05-1.18)</td>
<td>1.31 (1.23-1.39)</td>
<td>1.60 (1.52-1.69)</td>
</tr>
<tr>
<td>Variceal hemorrhage</td>
<td>2.03 (1.90-2.16)</td>
<td>1.83 (1.71-1.95)</td>
<td>1.70 (1.60-1.82)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>2.44 (2.28-2.60)</td>
<td>2.53 (2.37-2.70)</td>
<td>3.07 (2.86-3.30)</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>2.06 (1.75-2.43)</td>
<td>2.31 (1.96-2.73)</td>
<td>1.43 (1.20-1.71)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1.98 (1.82-2.15)</td>
<td>1.79 (1.63-1.96)</td>
<td>1.83 (1.67-2.01)</td>
</tr>
</tbody>
</table>

The Majority of Overt HE Patients Do Not Receive Proper Management Therapy After Discharge

- Analysis of medical and hospital claims
  - Outpatients who had ≥1 OHE episodes from 2009 to 2011 during a 3-year period
- >60% of patients did not receive ongoing prophylactic therapy to reduce risk of HE recurrence after discharge

Neff GW, Frederick RT. *Hepatology*. 2012;56(suppl 1):945A.
Reducing 30 Day Readmission By Intervention Phase

- **Electronic phase**
  - Checklist items incorporated into electronic provider order system

- **Check list phase**
  - QI checklist prompted medication review and dosing

### Reasons for 30-day Readmission By Intervention Phase

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Electronic n=146</th>
<th>Checklist n=139</th>
<th>Control n=194</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **HE**
- **Infection**
- **GI bleeding**
- **Symptomatic ascites**
- **Other**

Impact of Rifaximin Treatment on Hospital Resource Utilization

Mean Number of Admissions Prior to Rifaximin Initiation (N=326)

Data from a retrospective study of 326 patients from 7 UK liver treatment centers. Orr JG et al. Liver Int. 2016;36(9):1295-1303.
Impact of Rifaximin Treatment on Hospital Resource Utilization

Mean Length of Emergency Hospital Admissions (N=326)

Data from a retrospective study of 326 patients from 7 UK liver treatment centers. Orr JG et al. Liver Int. 2016;36(9):1295-1303.
Reasons for Readmission

**Patient Factors**
- Frailty
- Malnutrition
- Home situation
- Communication issues
- Transplant candidacy

**Medical Factors**
- Polypharmacy
- Psychological
- Comorbidities

**System Factors**
- Inpatient care
- Goals of care
- Discharge instructions
- Outpatient care
- Multidisciplinary management

Changes in Resting-State Functional MR Imaging

Healthy control subjects

Cirrhotic patients without MHE and without previous OHE

Cirrhotic patients with current MHE and without previous OHE

Cirrhotic patients with previous OHE

Learning Impairment in Patients with Cirrhosis with a Previous Episode of OHE

Patients With Cirrhosis Without Prior OHE Episode

Greater Decline in Brain Volume in Patients with History of HE After Liver Transplantation

Decreased Cognitive Functions Before and After Liver Transplant According to History of Overt HE

### Employment in Liver Transplant Recipients, in the United States

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Number</th>
<th>Follow-up (Months)</th>
<th>Mean Age (Years)</th>
<th>Return to Work (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowling et al.¹ (2004)</td>
<td>152</td>
<td>53</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Rongey et al.² (2005)</td>
<td>186</td>
<td>41</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Sahota et al.³ (2006)</td>
<td>105</td>
<td>34</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>Saab et al.⁴ (2007)</td>
<td>308</td>
<td>52</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Huda et al.⁵ (2012)</td>
<td>21,942</td>
<td>&lt;24</td>
<td>-</td>
<td>45</td>
</tr>
<tr>
<td>Duffy et al.⁶ (2010)</td>
<td>77</td>
<td>&gt;240</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>Gorevski et al.⁷ (2011)</td>
<td>91</td>
<td>-</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td><strong>Weighted</strong></td>
<td>22,861</td>
<td></td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

Conclusions

• Hepatic encephalopathy is an economic and social burden
  – Increased burden is realized not only by patients but also experienced by caregivers.

• Hepatic encephalopathy is an important cause of hospital readmission

• Hepatic encephalopathy is not a completely benign complication of cirrhosis
  – It may affect future learning that may persist even after liver transplantation
General Discussion/ Q&A
For more information or for additional CME offerings, please visit:
www.chronicliverdisease.org