Clinical Advances in the Management of Cirrhotics
Program Disclosure

• This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Purdue University College of Pharmacy and the Chronic Liver Disease Foundation. Purdue University School of Pharmacy is accredited by the ACCME to provide continuing medical education for physicians.

• This program is supported by an educational grant from Salix Pharmaceuticals.
Educational Objectives

• Discuss the natural history and complications of cirrhosis including management options

• Review the benefits of adding rifaximin to lactulose in the treatment of hepatic encephalopathy
The prevalence of cirrhosis, both worldwide and in the US, is unknown

- Compensated cirrhosis often goes undetected for prolonged periods of time

Experts estimate that up to 1% of the population (~3 million) may have histological cirrhosis

Cirrhosis Was the Most Common Reason for Liver Transplant in 2007

N = 6223 Recipients of Deceased Donor Livers

Wait List and Transplant Activity for Liver 1999–2008

Number of Patients

Year

On Waiting List Annually
Received Transplants Annually
Died While on Waiting List Annually

Etiology of Cirrhosis

• Cirrhosis can result from:
  – Alcohol-related liver disease (~60% to 70% of cases)
  – Chronic hepatitis C
  – Chronic hepatitis B
  – Chronic hepatitis B and D
  – Nonalcoholic fatty liver disease (NAFLD; ~10% of cases)
  – Autoimmune hepatitis
  – Drugs, toxins, and infections

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

Natural History of Cirrhosis

• Once decompensation occurs, median survival is approximately 2 years

• Most commonly reported causes of death:
  – Hepatorenal syndrome
  – Sepsis
  – Variceal hemorrhage
  – HCC

## Classification of Cirrhosis Severity Determinants for Child-Turcotte-Pugh (CTP)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Grade 1 - 2 (or precipitant-induced)</td>
<td>Grade 3 - 4 (or chronic)</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild/Moderate (diuretic-responsive)</td>
<td>Severe (diuretic-refractory)</td>
</tr>
<tr>
<td><strong>Bilirubin (mg/dL)</strong></td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td><strong>Albumin (g/dL)</strong></td>
<td>&gt;3.5</td>
<td>2.8 - 3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td><strong>Prothrombin Time</strong></td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

### Total Numerical Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Child-Pugh Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 6</td>
<td>A</td>
</tr>
<tr>
<td>7 - 9</td>
<td>B</td>
</tr>
<tr>
<td>10 - 15</td>
<td>C</td>
</tr>
</tbody>
</table>

Patients in Class A are considered "compensated"
Patients in Classes B and C are considered "decompensated"

Classification of Cirrhosis Severity
Model for End Stage Liver Disease score

• MELD - determines the severity of liver disease based on:
  – serum bilirubin,
  – serum creatinine
  – international normalized ration (INR)
    • developed in 2002 by UNOS

• Calculation:
  – \([0.957 \times (\text{Serum creatinine mg/dL}) + 0.378 \log_e (\text{Total bilirubin mg/dL}) + 1.12 \log_e (\text{INR}) + 0.64] \times 10\)

• Range: 6 – 40
  – equates to estimated 3-month survival rates from 90% to 7% respectively
Decompensated Cirrhosis

- Primary complications include:
  - Ascites
  - Jaundice
  - Variceal hemorrhage
  - Portosystemic encephalopathy

- Other possible complications include:
  - Spontaneous bacterial peritonitis
  - Hepatic hydrothorax
  - Hepatorenal syndrome
  - Portopulmonary hypertension
  - Hepatocellular carcinoma
  - Portal vein thrombosis

Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities

Stage 1
- Compensated
- NO VARICES
- NO ASCITES
- 1% death

Stage 2
- Varices
- NO ASCITES
- 3.4% death

Stage 3
- Ascites ± Varices
- 20% death

Stage 4
- Bleeding ± Ascites
- 57% death

Portal Hypertension
Blood Supply of The Liver


Increased Resistance
(Architectural changes secondary to fibrous tissue formation; active vasoconstriction due to decrease in formation of endogenous NO)

Increased Blood Flow
(Splanchnic arteriolar vasodilation)

Increased Portal Pressure

↑Resistance x ↑Flow = Portal Hypertension

Consequences of portal hypertension produce symptoms:

- Gastroesophageal varices
- Ascites
- Enlarged spleen
- Hepatic encephalopathy
Gastroesophageal Varices
Gastroesophageal Varices

- Gastroesophageal varices present in ~50% of patients with cirrhosis
  - Presence correlates with severity of liver disease
  - 40% of Child A patients have varices
  - 85% of Child C patients have varices

- Cirrhotic patients without varices develop them at a rate of 8% per year
  - Patients with small varices develop large varices at a rate of 8% per year

Gastroesophageal Variceal Hemorrhage

- Occurs at a yearly rate of 5% to 15%
- Most important predictor of hemorrhage is size of varices
- Other predictors of hemorrhage are:
  - Decompensated cirrhosis (Child B/C)
  - Endoscopic presence of red wale marks
- Associated with a mortality of ≥20% at 6 weeks
- Bleeding ceases spontaneously in ≤40% of patients

Esophagogastroduodenoscopy

- **No varices**
  - Repeat endoscopy in 3 years (well compensated); in 1 year if decompensated
  - No beta-blocker prophylaxis

- **Small varices (<5 mm), Child B/C, red wales**
  - Beta-blocker prophylaxis

- **Medium or large varices**
  - Child Class A, no red wales: Beta blockers
  - Child class B/C, red wales: Beta blockers, or endoscopic band ligation

Management of Acute Hemorrhage

• Patients with suspected acute variceal hemorrhage require intensive-care unit setting for resuscitation and management

• Acute GI hemorrhage requires:
  – Intravascular volume support
  – Blood transfusions
  – Maintaining hemoglobin of ~8 g/dL

• Institute short-term (7-day) antibiotic prophylaxis

• Initiate therapy with somatostatin (or its analogs)

• Perform esophagogastrroduodenoscopy within 12 hours; treat with endoscopic band ligation or sclerotherapy

Management of Acute Hemorrhage (cont)

- TIPS (transjugular intrahepatic portosystemic shunt) indicated if hemorrhage uncontrolled or recurrent bleeding despite pharmacologic and endoscopic therapy

- Balloon tamponade should be temporary measure used prior to more definitive therapy

Bacterial Infection and Variceal Bleeding

- Variceal bleeding associated with increased risk of bacterial infection
  - SBP (spontaneous bacterial peritonitis), urinary tract infection, pneumonia or bacteremia

- Develops in 20% of patients within 48 hours and in 35% to 66% of patients within 2 weeks

- Compared to patients without infection, presence of infection is associated with
  - Failure to control bleeding (65% vs 15%)
  - Early rebleeding
  - Mortality (40% vs 3%)

• Prophylactic ofloxacin vs antibiotics only at diagnosis of infection
• ↓ infections (2/59 vs 16/61)
• Less rebleeding within 7 days
• ↓ blood transfusions for rebleeding
• Prophylactic antibiotics recommended in management of acute variceal hemorrhage
Ascites
Ascites

- Most common complication of cirrhosis
- Only occurs when portal hypertension has developed
- ~60% of patients with compensated cirrhosis develop ascites within 10 years
- 50% mortality rate within 3 years
- Patients should generally be considered for liver transplantation referral

Prognosis of Patients with Cirrhosis at Onset of Ascites

## AASLD Practice Guidelines: Ascitic Fluid Analysis

<table>
<thead>
<tr>
<th>Routine</th>
<th>Optional</th>
<th>Unusual</th>
<th>Unhelpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count and differential</td>
<td>Culture in blood culture bottles</td>
<td>Acid-fast bacteria smear and culture</td>
<td>pH</td>
</tr>
<tr>
<td>Albumin</td>
<td>Glucose</td>
<td>Cytology</td>
<td>Lactate</td>
</tr>
<tr>
<td>Total protein</td>
<td>Lactose dehydrogenase</td>
<td>Triglyceride</td>
<td>Cholesterol</td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td>Bilirubin</td>
<td>Fibronectin</td>
</tr>
<tr>
<td></td>
<td>Gram’s stain</td>
<td></td>
<td>Glycosaminoglycans</td>
</tr>
</tbody>
</table>
Management of Ascites

First-Line Therapy

Tense ascites

- Paracentesis
- Sodium restriction (<2 Gm/24 Hrs) and diuretics*

Non-tense ascites

*Diuretics: Spironolactone 100 mg/day, furosemide 40 mg/day or bumetanide 1 mg/day; uptitrate stepwise to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as tolerated

Second-Line Therapy

- Repeated large volume paracentesis (LVP)†
- TIPS
- Liver Transplantation

†Albumin infusion of 6-8 gm/liter of fluid removed is a consideration for repeated LVP; post-paracentesis albumin infusion may not be necessary for < 5 liters removed

Adapted from Runyon BA. *Hepatology.* 2009; 49:2087-2107.
Spontaneous Bacterial Peritonitis
(SBP)
Spontaneous Bacterial Peritonitis: Diagnosis

- Diagnosis of SBP:
  - Positive ascitic fluid bacterial culture
  - Elevated ascitic fluid absolute PMN count (ie, \( \geq 250 \) cells/mm\(^3 \) [0.25 x 10\(^9\)/L])
  - No evident intra-abdominal source of infection

Secondary Bacterial Peritonitis: Diagnosis

• Diagnosis of secondary bacterial peritonitis:
  – PMN count ≥250 cells/mm$^3$ (usually many thousands)
  – Multiple organisms on Gram stain and culture
  – Total WBC usually >10,000/mL
  – At least 2 of the following:
    • Total protein >1g/dL
    • Lactate dehydrogenase > upper limit of normal for serum
    • Glucose <50 mg/dL
  – Ascitic fluid carcinoembryonic antigen >5 ng/mL or ascitic fluid alkaline phosphatase >240 U/L also accurate in detecting gut perforation

## Prevention of SBP – Prophylaxis

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dose /Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>400 mg/day orally</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1g/day IV for 7 days</td>
</tr>
<tr>
<td>Double-strength trimethoprim/sulfamethoxazole</td>
<td>5 doses/week</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750 mg as single oral dose/week</td>
</tr>
</tbody>
</table>

- **High ascitic fluid protein**: $>1$ gram/dL
- **Low ascitic fluid protein**: $\leq 1$ gram/dL

Intermittent dosing of prophylactic antibiotics may select resistant flora; daily dosing preferred.
Renal Dysfunction
Renal Injury in Cirrhosis

Hospitalized patients with cirrhosis

Chronic renal failure
1%

ARF / AKI
19%

Pre-renal
68%

Intra-renal (ATN, GMN)
32%

Post-renal (obstructive)
<1%

Volume-responsive
66%
- Infection
- Hypovolemia
- Vasodilators
- Other

Not volume-responsive

HRS type 1
25%

HRS type 2
9%


<table>
<thead>
<tr>
<th>ARF: Acute renal failure</th>
<th>GMN: Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN: Acute tubular necrosis</td>
<td>AKI: Acute kidney injury</td>
</tr>
<tr>
<td>HRS: Hepatorenal syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Survival Is Decreased With Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction

Survival Among Patients With Cirrhosis and Hepatorenal Syndrome

Survival Is Decreased With Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction

Survival Among Patients With Cirrhosis and Hepatorenal Syndrome

Prevention of Acute Renal Injury in Cirrhotics

- Prevent/treat volume depletion or vasodilatation
  - Careful use of diuretics
  - Avoidance of diarrhea with use of lactulose
  - Use of albumin after large-volume paracentesis

- Avoid use of aminoglycosides and NSAIDs

- Aggressively treat hypovolemia/hypotension occurrence
Hepatorenal Syndrome
Hepatorenal Syndrome: Risk Factors

- Development of bacterial infections, particularly SBP, is the most important risk factor
  - Hepatorenal syndrome develops in ~30% of patients with spontaneous bacterial peritonitis
  - Treatment with albumin infusion/antibiotics reduces the risk of developing hepatorenal syndrome and improves survival

Hepatorenal Syndrome: Prognosis

- The prognosis of hepatorenal syndrome is poor
  - Average median survival ~ 3 months
  - High MELD score and type 1 hepatorenal syndrome are associated with very poor prognosis
    - Median survival of patients with untreated type 1 hepatorenal syndrome is ~ 1 month
Hepatic Encephalopathy (HE)
Utilization and Outcome of Critical Care in Patients With Cirrhosis

- Reviewed 2006 Nationwide Inpatient Sample (NIS) of the Health Care Utilization Project to identify hospitalization records showing cirrhosis and/or portal hypertensive complications

- 65,072 discharge records met the inclusion criteria which projected to 317,300 cirrhosis hospitalizations (95% CI, 300,100-334,400)
  - Of these, 26,300 (95% CI, 24,400-28,200) entailed critical care

- Characteristics of patients requiring critical care
  - Age: 55.5 years
  - Male: 63%
  - Ascites: 49%
  - Encephalopathy: 41%
  - Variceal bleeding: 14%
  - Hepatorenal syndrome: 12%

Increased risk of death and hospital charges associated with complications

<table>
<thead>
<tr>
<th>Factor</th>
<th>In-Hospital Death</th>
<th>Total Charges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P</td>
</tr>
<tr>
<td>ICU care</td>
<td>13.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>6.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Variceal Hemorrhage</td>
<td>0.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HCC</td>
<td>1.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Prevalence of Hepatic Encephalopathy

- Two forms of HE are recognized: **Overt** and **Minimal** based on the nature and severity of clinical manifestations

  - **Overt hepatic encephalopathy (OHE)** occurs in:
    - 30 to 45% of cirrhotic patients
    - 10 to 50% of patients with TIPS

  - **Minimal hepatic encephalopathy (MHE)** affects approximately 20 to 60% of patients with liver disease

Overt Hepatic Encephalopathy (OHE)

- Associated with a poor prognosis

- Retrospective review of 111 cirrhotic patients for 12±17 months following first episode of acute OHE:
  - 82 (74%) died during follow-up period
  - Survival probability
    - 42% at 1 year
    - 23% at 3 years

Diagnosis of OHE

- Clinical recognition of the distinctive neurologic features
- Knowledge that underlying cirrhosis is present
- Exclusion of all other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Grading systems to evaluate mental status
- Portal-systemic encephalopathy score (PSE score; Conn score) to evaluate overall severity

Adapted from:
# Neurologic Manifestations of OHE

<table>
<thead>
<tr>
<th>Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confusion or coma</td>
<td>• Cognitive deficits detected by special testing</td>
</tr>
<tr>
<td>• Asterixis</td>
<td>• Babinski sign</td>
</tr>
<tr>
<td>• Loss of fine motor skills</td>
<td>• Slow, monotonous speech</td>
</tr>
<tr>
<td>• Hyperreflexia</td>
<td>• Extrapyramidal-type movement disorders</td>
</tr>
<tr>
<td></td>
<td>• Clonus</td>
</tr>
<tr>
<td></td>
<td>• Decerebrate posturing</td>
</tr>
<tr>
<td></td>
<td>• Decorticate posturing</td>
</tr>
<tr>
<td></td>
<td>• Hyperventilation</td>
</tr>
<tr>
<td></td>
<td>• Seizures*</td>
</tr>
</tbody>
</table>

*Seizures seen primarily in type A HE.

Adapted from Mullen KD. *Semin Liver Dis.* 2007;27(suppl 2):3-9.
Treatment of OHE
Treatment Goals for OHE

- 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

Treatment Options for OHE

- Reduction of nitrogenous load from gut
  - Bowel cleansing
  - Non-absorbable disaccharides (lactulose)
  - Antibiotics (rifaximin, metronidazole)*
  - Agents that bind NH$_3$ in the gut
    - Na benzoate
    - Na phenylacetate
    - Na phenylbutyrate

- Drugs that affect neurotransmission (flumazenil, bromocriptine)

- Manipulation of splanchnic circulation (occlusion of portal-systemic collaterals)
  - Occlude TIPS shunt if present

* Neomycin (historical interest).

# Current Therapy Options for HE

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
</table>
| Lactulose | Poorly absorbed disaccharide | • Decrease blood ammonia concentration  
• Prevention and treatment of portal-systemic encephalopathy |
| Rifaximin | Non-aminoglycoside semi-synthetic, nonsystemic antibiotic | Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age. |
| Neomycin | Aminoglycoside antibiotic | Adjuvant therapy in hepatic coma |
| Metronidazole | Synthetic antiprotozoal and antibacterial agent | Not approved for HE |
| Vancomycin | Aminoglycoside antibiotic | Not approved for HE |

Older Oral Antibiotics

• Potential for adverse effects often precludes their use as first-line therapy for HE
  – Neomycin: Ototoxicity and nephrotoxicity
  – Metronidazole: Peripheral neurotoxicity
  – Vancomycin: Increased risk of bacterial resistance and renal toxicity

• Increased risk of serious adverse events limits use in prolonged therapy

Lactulose

• Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment

• Mechanism of action:
  – A non-absorbable dissacharide that is fermented in the colon
  – Metabolism by the bacterial flora in the colon to lactic acid lowers the colonic pH
  – Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume

Bajaj JS. *Aliment Pharmacol Ther* 2010;31:537-547.
Lactulose (cont)

- Administered orally, by mouth or through a nasogastric tube or via retention enemas

- Dose: 30-90 mL/day or 20 to 60 g/day, titrated to achieve 2 to 3 soft stools per day with a pH below 6

- Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence

- Systematic review of clinical studies found insufficient evidence to support or refute the use of lactulose for HE

Ferenci P. Semin Liver Dis. 2007;27(suppl 2):10-17.
Bajaj JS. Aliment Pharmacol Ther 2010;31:537-547.
Rifaximin

- Minimally absorbed (<0.4%) oral antibiotic
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
- No clinical drug interactions reported
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Approved for overt recurrent HE risk reduction in patients ≥18 years of age
- In registration trials, 91% of patients were given lactulose concomitantly

Rifaximin 550 mg BID n=140

Discontinued n=52 (37%)
- Breakthrough HE: n=28
- Adverse event: n=8
- Death: n=6
- Patient request: n=6
- Exclusion criteria: n=1
- Other: n=3

Completed Study n=88

Rifaximin Trial: Randomization and Follow-Up

Randomization 1:1 N=299 (Randomized Controlled Trial)

Placebo n=159

Discontinued n=93 (58%)
- Breakthrough HE: n=69
- Patient request: n=9
- Adverse event: n=7
- Death: n=3
- Exclusion criteria: n=3
- Other: n=2

Completed Study n=66

Rifaximin Trial: Eligibility Criteria

- Age ≥18 years
- ≥2 episodes of overt HE (Conn score, ≥2) associated with hepatic cirrhosis during the previous 6 months
- Remission (Conn score, 0 or 1) at enrollment
- Score ≤25 on the MELD scale
- Episodes of HE precipitated by GI hemorrhage requiring transfusion of ≥2 units of blood, medication use, renal failure requiring dialysis, or injury to the CNS were not counted as previous episodes

### Rifaximin Trial: Lactulose Use at Baseline and During Study

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin (n=140)</th>
<th>Placebo (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose use at baseline—no (%)*</td>
<td>128 (91.4%)</td>
<td>145 (91.2%)</td>
</tr>
<tr>
<td>Lactulose use during study—no (%)*</td>
<td>128 (91.4%)</td>
<td>145 (91.2%)</td>
</tr>
</tbody>
</table>

*During the study, 3 patients discontinued therapy with lactulose and 3 patients started therapy with lactulose (1 in the rifaximin group and 2 in the placebo group).
Proportion of Patients Without Breakthrough HE (%)

Rifaximin* (77.9%)
Placebo* (54.1%)

*Rifaximin 550 mg or placebo twice daily

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)
P<0.001

Rifaximin Trial: Time to First HE-Related Hospitalization Key Secondary End Point

- Rifaximin\(^*\) (86.4%)
- Placebo\(^*\) (77.4%)

*Rifaximin 550 mg or placebo twice daily
Hazard ratio with rifaximin, 0.50 (95% CI, 0.29–0.87)
\(P<0.0129\)

Rifaximin Trial: Time to First Breakthrough HE Episode Subgroup Analysis

- Degree to which rifaximin reduced risk of breakthrough episodes was consistent across subgroups including:

  - Geographic region
  - Sex
  - Age (<65 yr vs ≥65 yr)
  - Race or ethnic group
  - MELD score
  - Conn score
  - Lactulose use at baseline
  - Diabetes
  - Duration of remission
  - No. of HE episodes in previous 6 mo
  - TIPS
  - Time to first breakthrough HE episode

### Rifaximin Trial: Side Effects Similar to Placebo

- Incidence of adverse events did not differ significantly between 2 study groups ($P>0.05$ for all comparisons)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rifaximin (n=140)</th>
<th>Placebo (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>112 (80.0)</td>
<td>127 (79.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14.3)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (10.7)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12.1)</td>
<td>18 (11.3)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21 (15.0)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Ascites</td>
<td>16 (11.4)</td>
<td>15 (9.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (12.9)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10.0)</td>
<td>17 (10.7)</td>
</tr>
</tbody>
</table>

Minimal Hepatic Encephalopathy (MHE)
Minimal Hepatic Encephalopathy

- Identified in up to 60% of patients with cirrhosis tested\(^1\)
- Significantly diminishes quality of life\(^2\)
- Significantly diminishes working and earning capacity in blue-collar workers\(^2\)
- Increased progression to OHE\(^3\)
- Impairs driving on structured driving tests\(^4,5\)
- Increases risk of traffic accidents and violations\(^6\)

## Diagnostic Methods for MHE

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal neuropsychologic</td>
<td>Established and well-recognized clinical significance</td>
<td>• Expensive&lt;br&gt;• Time consuming</td>
</tr>
<tr>
<td>assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short neuropsychologic</td>
<td>• Easy to administer in office setting&lt;br&gt;• Inexpensive&lt;br&gt;• Rapid results&lt;br&gt;• High sensitivity for discerning minimal HE from other encephalopathies</td>
<td>• Test often copyrighted&lt;br&gt;• Limited access</td>
</tr>
<tr>
<td>batteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computerized tests (CFF, ICT,</td>
<td>• Easy to apply</td>
<td>• Limited data on diagnostic significance&lt;br&gt;• Require standardization</td>
</tr>
<tr>
<td>reaction times, etc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurophysiologic tests (EEG,</td>
<td>• Allows for objective repeat testing</td>
<td>• Equipment&lt;br&gt;• Limited data on diagnostic significance</td>
</tr>
<tr>
<td>spectral EEG, P300)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CFF- critical flicker frequency; ICT-inhibitory control test; EEG-electroencephalography; P300-auditory event-related evoked potential.

MHE: Associated With Motor Vehicle Crashes Predictive Accuracy of Diagnostic Testing

Percentage of patients with crashes by SELF-REPORT according to MHE status and diagnostic test (n=120)

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHE Inhibitory Control Test</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>MHE Standard Psychometric Test</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

\[ P = 0.0004 \]

Percentage of patients with crashes by DOT according to MHE status and diagnostic test (n=167)

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHE Inhibitory Control Test</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>MHE Standard Psychometric Test</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

\[ P = 0.004 \]

\[ P = 0.37 \]

Rifaximin Improves Cognitive Functions and Health-Related QoL in Patients With MHE

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin* (n=49)</th>
<th>Placebo (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-at 2 weeks</td>
<td>28/49 (57.1%)†</td>
<td>8/45 (17.8%)</td>
</tr>
<tr>
<td>-at 8 weeks</td>
<td>37/49 (75.5%)†</td>
<td>9/45 (20%)</td>
</tr>
<tr>
<td>Mean number of abnormal NP tests‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-baseline</td>
<td>2.35 (2.17-2.53)</td>
<td>2.31 (2.03-2.59)</td>
</tr>
<tr>
<td>-at 2 weeks</td>
<td>1.29 (1.02-1.56) P=0.002</td>
<td>2.03 (1.74-2.31)</td>
</tr>
<tr>
<td>-at 8 weeks</td>
<td>0.81 (0.61-1.02) P=0.000</td>
<td>1.97 (1.69-2.25) P&gt;0.05</td>
</tr>
<tr>
<td>Mean Z score§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-baseline</td>
<td>-2.54 (-2.81 - -2.27)</td>
<td>-2.61 (-2.89 - -2.33)</td>
</tr>
<tr>
<td>-at 8 weeks</td>
<td>-1.44 (-1.84 - -1.03) P=0.000</td>
<td>-2.26 (-2.55 - -1.98) P&gt;0.05</td>
</tr>
<tr>
<td>Mean Total Sickness Impact Profile Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-baseline</td>
<td>11.67 (10.31-13.03)</td>
<td>9.86 (8.66-11.06)</td>
</tr>
<tr>
<td>-at 8 weeks</td>
<td>6.45 (5.59-7.30) P=0.000</td>
<td>8.51 (7.35-9.67) P=0.82</td>
</tr>
</tbody>
</table>

*1200 mg/day for 8 weeks.
† P<0.0001, rifaximin compared to placebo.
‡ 5 NP tests (2 number and figure connection, picture completion, digit symbol, block design).
§ Difference in SD between observed and expected scores.

Rifaximin Improves Driving Simulator Performance in Patients With MHE

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin* (n=21)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in speeding tickets†</td>
<td>-2.46‡</td>
<td>0.46</td>
</tr>
<tr>
<td>% who reduced speeding tickets</td>
<td>81%‡</td>
<td>19%</td>
</tr>
<tr>
<td>Reduction in illegal turns on navigation†</td>
<td>-1.67‡</td>
<td>-0.43</td>
</tr>
<tr>
<td>% who reduced illegal turns</td>
<td>61%‡</td>
<td>21%</td>
</tr>
<tr>
<td>Improvement in mean cognitive Z score†</td>
<td>1.13‡</td>
<td>0.3</td>
</tr>
<tr>
<td>% who improved cognitive tests</td>
<td>91%‡</td>
<td>61%</td>
</tr>
</tbody>
</table>

• No change in either group in total/physical Sickness Impact Profile, ammonia, or MELD score.
• Sickness Impact Profile psychosocial score improved from 12 to 8 ($P=0.05$) in the rifaximin group compared to a change from 13 to 11 ($P=0.5$) in the placebo group.

*550 mg BID for 8 weeks.
†Test results at week 8 vs baseline.
‡Significantly better compared to placebo.

Bajaj JS et al. *Hepatology.* 2010;52(Suppl S1):330A.
HE Summary

• HE is very common in the cirrhotic patient

• Significantly diminishes quality of life

• Increases risk of traffic accidents due to neurologic manifestations

• Important to diagnose and manage