HOT TOPICS in Cirrhosis

Sunday, May 19, 2019
Manchester Grand Hyatt
Seaport Ballroom F-G-H
This program is supported by educational grants from Dova Pharmaceuticals, Inc., Mallinckrodt Pharmaceuticals, and Salix Pharmaceuticals.
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**Planning Committee Member**
Lisa D. Pedicone, PhD – Nothing to disclose.

**Faculty**
All faculty disclosures can be found in your meeting guide.
Breaking News in Chronic Liver Disease

Kimberly Brown, MD, FAST, FAAASLD, AGAF
Acute Hepatitis C on the Rise
CDC (2013-2016): Estimated HCV Prevalence Among Adults in the United States

- HCV antibody positive (including past and current infection)
  - Number: 4.1 million (95% CI 3.4-4.9)
  - Prevalence: 1.7% (95% CI 1.4-2.0)

- HCV RNA positive (including current infection)
  - Number: 2.4 million (95% CI 2.0-2.8)
  - Prevalence: 1.0% (95% CI 0.8-1.1)

Datasets analyzed: National Health and Nutrition Examination Survey (noninstitutionalized civilian population).
Combination of literature reviews and population size estimation approaches (incarcerated people, unsheltered homeless people, active-duty military personnel, and nursing home residents).

- New acute HCV infection in 2016
  - Reported cases (n=2967)
  - Estimated (n=41,200, adjusted for under-ascertainment and under-reporting)
- 3.5-fold increase in new cases since 2010
  - Reflects new infections associated with rising rates of injection-drug use
- Most newly acquired acute HCV infections occurred among young, white, PWIDs, who live in non-urban areas (i.e., Appalachian, Midwestern, and New England states)

Populations at Risk

Baby Boomers (born 1945-1965)
- **1960s**: Up to 300,000 cases of acute HCV per year; risk of exposure via blood transfusion up to 33%
- **1970s**: Volunteer donor system reduces risk of exposure via blood transfusion
- **1989**: HCV discovered
- **1992**: Widespread introduction of HCV antibody testing

People Who Inject Drugs (PWID)
- **1992**: Widespread introduction of HCV antibody testing
- **30-70% prevalence**

Geographic Areas Most at Risk for HCV

Counties Vulnerable to Outbreaks of HIV and Hepatitis C

CDC report identified >220 counties vulnerable to outbreaks of HIV and HCV among people who inject drugs

Risk Factors
- Unemployment rates
- Overdose deaths
- Prescription opioid sales

WHO Goal:
Global Elimination of Viral Hepatitis
Global Health Sector Strategy: Eliminate Viral Hepatitis as a Major Public Health Threat by 2030

Impact Targets

**Reduction in new infections by 90%**

Programmatic Targets

- **90%** of people infected are diagnosed
- **80%** of people diagnosed are treated
- **90%** coverage of BD and B3 doses (PAHO: 95%)
- **100%** of blood products are safe
- **90%** of injections in health facilities are safe

Reduction in deaths by 65%
HCV No Longer a Disease Limited to Baby Boomers

Data for New York State (excluding NYC).
Claims data for HCV Ab screening from a single large commercial payer (CPT and ICD-9 codes):
Screened (n=1,056,583); not screened (n=1,243,581).
Factors that increased the odds of getting screened: female gender, Medicare, presence of comorbidities.

Effectiveness of HCV Screening in the US (2010-2016)

- In the US, to meet the 2030 diagnosis targets, this means diagnosing at least
  - 110,000 cases/year until 2020
  - 89,000 cases/year between 2020-2024
  - >70,000 cases/year between 2025-2030
- At the current screening rate, 92% of US states are not on target to meet
  WHO screening goals of HCV elimination by 2030

Timeline to Achieve WHO Screening Target for HCV Elimination

Reach WHO Target by:
- 2030
- 2040
- 2050
- Beyond 2050

Claims data for HCV Ab screening from a single large commercial payer (CPT and ICD-9 codes):
Screened (n=1,056,583); not screened (n=1,243,581).
Factors that increased the odds of getting screened: female gender, Medicare, presence of comorbidities.
HCV Screening Is Straightforward: Algorithm for Screening/Diagnosis

- **Screening Test for Anti-HCV**
  - Negative: STOP
  - Positive: Test for Quantitative HCV RNA
    - Negative: Retest in 6 months
    - Positive: Genotyping testing also recommended
      - Refer to specialist for Disease Staging and Management Plan

HCV Continuum of Care Among PWIDs: Philadelphia Department of Health

- Random sample of newly reported HCV antibody positive persons (n=29,820; 2013-2017)
  - Interviewed and disclosed being a PWID (n=2390)
- Measurable gaps exist in the HCV continuum of care for PWIDs, especially those ≤35 years of age
  - Among those HCV RNA positive
    - Only 25% and 8% of PWIDs >35 and ≤35 years of age, respectively, were treated
- Need for enhanced navigation to services

Important New Treatment for Primary Biliary Cholangitis
Primary Biliary Cholangitis (PBC) is a chronic, progressive autoimmune disease.

Factors possibly associated with onset and perpetuation of bile-duct injury in PBC:

- Genetics
- Environment
- Immune response
- Bile duct damage

PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis.

Farnesoid X Receptor Signaling

Bile Acids (Primary ligands for FXR)

FXR (Hepatocytes, biliary epithelium, small bowel enterocytes, renal tubular cells, adrenal cells, adipocytes, beta cells)

↑ Gene Expression (BSEP, MDR3, MRP 2/3/4, OST α/β)
↓ Gene Expression (CYP7A1, NTCP, OATP)

Direct Effects

↑ Bile Acid Efflux

Indirect Effects

↓ Bile Acid Synthesis and Uptake

Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.
Obeticholic Acid (OCA): Approved FXR Agonist for PBC

• PBC: OCA is associated with statistically significant, clinically meaningful improvements
  – Biochemical criteria correlated with clinical benefit (alkaline phosphatase and bilirubin)
  – Markers of inflammation (C-reactive protein) and apoptosis (CK18)

• Nonalcoholic steatohepatitis (NASH): Phase 3 topline results released February 19th
  – OCA showed statistically significant improvement in liver fibrosis without worsening of NASH at 18 months
  – Very active research area; however, OCA is expected to be the first FDA approved drug for NASH
Long Term Side Effects Reduced with New Treatment for Hepatitis B
HBV Therapy Reduces Risk of Disease Progression

- Patients with HBV and first-onset complications of decompensated cirrhosis treated predominantly with lamivudine or entecavir

- Antiviral therapy improved transplant-free survival over mean follow-up of 49 mos \((P = 0.0098\) vs untreated)

*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, NE due to early event (death, LT, LTFU).

## Guidelines: What to Start as Initial HBV Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Preferred</th>
<th>Notes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>Yes</td>
<td>High potency, high genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>Yes</td>
<td>High potency, high genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>Yes</td>
<td>High potency, high genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>PegIFN</td>
<td>Should only be considered as initial therapy for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)</td>
<td>Less safe in pts with cirrhosis, contraindicated in pts with decompensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
<td></td>
</tr>
</tbody>
</table>

**ETV, TDF, TAF have very favorable safety and resistance profiles**

TAF= Tenofovir alafenamide  
TDF= Tenofovir disoproxil fumarate  
Chronic Hepatitis B: Newest Therapy (Tenofovir AF)

- Higher levels of TFV-diphosphate in target cells at lower doses than tenofovir DF
- Tenofovir AF has a lesser effect on the proximal renal tubule
- 90% lower TFV levels in plasma minimizes renal and bone effects while maintaining high potency for suppressing HBV

TFV= Tenofovir

TFV diphosphate levels in target cells are higher with Tenofovir AF at lower doses compared to tenofovir DF. Tenofovir AF has a lesser effect on the proximal renal tubule, resulting in 90% lower TFV levels in plasma, which minimizes renal and bone effects while maintaining high potency for suppressing HBV.
**Study 108 and 110 Pooled Analysis: TAF vs TDF at 144 Weeks**

**HBeAg-Negative**

- HBV DNA <29 IU/mL
  - TAF: 248/285 (87%)
  - TDF: 63/74 (85%)

  \[ p = 0.71 \]

**HBeAg-Positive**

- HBV DNA <29 IU/mL
  - TAF: 428/581 (74%)
  - TDF: 127/178 (71%)

  \[ p = 0.59 \]

<table>
<thead>
<tr>
<th></th>
<th>TAF</th>
<th>TDF</th>
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</thead>
<tbody>
<tr>
<td>HBeAg loss, n/N (%)</td>
<td>135/565 (24)</td>
<td>39/175 (22)</td>
</tr>
<tr>
<td>HBeAg seroconversion, n/N (%)</td>
<td>105/565 (19)</td>
<td>23/175 (13)</td>
</tr>
<tr>
<td>HBsAg loss, n/N (%)</td>
<td>9/857 (1)</td>
<td>3/251 (1)</td>
</tr>
<tr>
<td>HBsAg seroconversion, n/N (%)</td>
<td>7/857 (1)</td>
<td>1/251 (&lt;1)</td>
</tr>
</tbody>
</table>

No resistance to TAF and TDF was detected through Week 144

ALT Normalization at Week 144

There were higher rates of ALT normalization by AASLD 2018 criteria in patients on TAF compared to TDF.

AASLD 2018 criteria ULN: males ≤ 35 U/L, females ≤ 25 U/L.
There were significantly smaller decreases in eGFR$_{CG}$ and smaller changes in proximal tubular markers with TAF compared to TDF at Week 144.

*From 2-sided Wilcoxon rank-sum test.
Changes in Bone Mineral Density (BMD) in Patients Over 144 Weeks

There were significantly less declines in hip BMD in patients on TAF compared to TDF

*From analysis of variance model including treatment as fixed effect.
†From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).
E/C/F/TAF vs E/C/F/TDF in HIV Infection: Wk 144 Renal and Bone Outcomes

- Randomized phase III trials conducted in treatment-naive HIV-infected pts with eGFR ≥ 50 mL/min

<table>
<thead>
<tr>
<th>Renal Events Leading to Discontinuation, n</th>
<th>E/C/F/TAF (n = 866)</th>
<th>E/C/F/TDF (n = 867)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal renal tubulopathy</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cr elevation or eGFR decrease</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bladder spasm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

E, elvitegravir; C, cobicistat; F, emtricitabine; TAF, tenofovir alafenamide.

*p values calculated using analysis of variance model including treatment as a fixed effect.
Clinical Case Forum I: Current and Emerging Management Approaches for the Cirrhotic Patient with Thrombocytopenia

Sammy Saab, MD, MPH, AGAF, FACG, FAAASLD
47 year old male with decompensated alcohol-related cirrhosis

47 year old gentleman with decompensated alcohol-related cirrhosis returns to clinic after being recently admitted and banded for bleeding esophageal varices.

- Pertinent admission labs:
  - HB 5.2, PLT 32, INR 1.4, TB 1.2
  - Required 6 bands.
  - Transfused PRBCs and Platelets

- Follow up outpatient endoscopy with additional banding recommended.
Patient Case

47 year old male with decompensated alcohol-related cirrhosis

- Family History
  - No family history of liver disease.

- Social History:
  - No history of injectable drugs. Stopped drinking alcohol about 3 years ago. Not currently working.
47 year old male with decompensated alcohol-related cirrhosis

**Past Medical History**

**PMH:**
- Alcohol related cirrhosis
- Diabetes
- No hypercoagulable state

**PSH:**
- Noncontributory
47 year old male with decompensated alcohol-related cirrhosis

- Medications:
  - Propranolol
  - Diabetes

- Allergies:
  - None
47 year old male with decompensated alcohol-related cirrhosis

- 98.7 temp; 65 heart rate, 110/65.
- General: Overweight.
- Heart: Regular rate and rhythm. No murmurs, rubs, or gallops.
- Lungs: Clear to auscultation. No wheezes, rhonchi, or rales.
- Skin: Spider angiomas and palmar erythema. No caput medusa. No fluid wave.
- Extremity: No edema.
47 year old male with decompensated alcohol-related cirrhosis

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>2.7</td>
</tr>
<tr>
<td>HB</td>
<td>10.9</td>
</tr>
<tr>
<td>PLT</td>
<td>37</td>
</tr>
<tr>
<td>ALB</td>
<td>3.8</td>
</tr>
<tr>
<td>TB</td>
<td>1.4</td>
</tr>
<tr>
<td>AST</td>
<td>52</td>
</tr>
<tr>
<td>ALT</td>
<td>48</td>
</tr>
<tr>
<td>AP</td>
<td>119</td>
</tr>
<tr>
<td>INR</td>
<td>1.2</td>
</tr>
<tr>
<td>Na</td>
<td>137</td>
</tr>
<tr>
<td>CR</td>
<td>1.1</td>
</tr>
<tr>
<td>MELD</td>
<td>11</td>
</tr>
</tbody>
</table>
Thrombocytopenia in CLD

- Thrombocytopenia is a common problem in patients with cirrhosis (platelets <100,000)
  - Estimated to affect up to 70% of CLD patients
  - Extent worsens with severity of portal hypertension and disease
  - Patients may be ineligible for elective surgical or diagnostic procedures due to risk of bleeding
  - Increases risk of mortality
  - Increases risk of poor clinical outcomes

Etiologies of Thrombocytopenia in Chronic Liver Disease

- Splenic sequestration secondary to portal hypertension
- Direct bone marrow suppression secondary to viruses, alcohol, iron, or drugs
- Increased destruction secondary to anti-platelet antibodies, shear stress, infection, or increased fibrinolysis
- Decreased production of thrombopoietin (TPO) by the liver

47 year old male with decompensated alcohol-related cirrhosis

- Abdominal ultrasound
  - Nodular liver
  - No hepatocellular carcinoma
  - No ascites
  - Portal vein patent
History of Present Illness – July 2018

47 year old male with decompensated alcohol-related cirrhosis

- Patient referred to outpatient EGD with banding.
- Because of thrombocytopenia, platelet transfusion also ordered.
Platelet Transfusions: Benefits and Considerations

**Benefits:**
- Prevent the risk of bleeding:
  - Thrombocytopenic patients
  - Patients with platelet dysfunction
- Control bleeding in patients with active bleed

**Considerations:**
- Risk of infections
- Hemolytic/Febrile non-hemolytic/Allergic/Anaphylactic Reactions
- Refractoriness (immune vs nonimmune)
- Storage logistics
- Patient scheduling logistics
- Limited shelf life
- Cost
- Supply vs demand
47 year old male with decompensated alcohol-related cirrhosis

History of Present Illness – July 2018

• Patient returns for follow up
• Said he will never undergo endoscopy again
  – Developed platelet transfusion reaction with fever and rigor
• Discussed risks of recurrent esophageal variceal bleeding
Current Landscape in Patients with Thrombocytopenia and CLD

• Patients require 1-3 procedures annually
• Different procedures are associated with different risks of bleeding
  – Procedures are required to clinically manage patients with CLD
  – Thrombocytopenia can lead to serious uncontrolled bleeding in these patients negatively impacting clinical care
    • Prolonged hospitalizations
    • Serious complications
    • Poor clinical outcomes
• Historically, the only treatment option was platelet transfusion

Thrombopoietin Receptor Agonists

- Mimics effects of thrombopoietin (TPO) to increase platelet production
- Binds to a different region of the TPO receptor and does not block native TPO
- Predictable PK/PD profile
Avatrombopag Phase 3 Study Design
ADAPT-1 & ADAPT-2 (N=435)

PRE-RANDOMIZATION
VISIT 1
Screening Period
Day -14 to -1

Low Baseline Platelet Count Cohort
mean Baseline PC
<40 x 10^9/L

High Baseline Platelet Count Cohort
mean Baseline PC
40 to <50 x 10^9/L

RANDOMIZATION
(2:1 avatrombopag:placebo)

VISIT 2
BASELINE DAY 1

VISIT 3
TREATMENT DAY 2-5

VISIT 4
PROCEDURE* DAY 10-13

VISIT 5
7 DAYS POST PROCEDURE

VISIT 6
DAY 35

FOLLOW-UP

60 mg AVATROMBOPAG qd x 5 Days

PLACEBO

40 mg AVATROMBOPAG qd x 5 Days

PLACEBO

*Platelet transfusions were not mandatory
AASLD 2017
Study Endpoints

• Primary Endpoint:
  – Proportion of patients who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure

• Secondary Endpoints:
  – Proportion of patients achieving target platelet count of $\geq 50 \times 10^9$/L on Procedure Day
  – Change in platelet count from Baseline to Procedure Day
  – Safety
RESULTS: Patients Who Did Not Require Platelet Transfusion or Rescue Procedure for Bleeding

Adapt 1 (231 patients)

- Low Baseline Platelet Count Cohort: <40 x 10^9/L
  - Placebo (n=48): 48% (22.9% p<0.0001)
  - Avatrombopag (60 mg) (n=90): 65.6% (p<0.0001)
  - Avatrombopag (40 mg) (n=93): 88.1%

- High Baseline Platelet Count Cohort: 40 to <50 x 10^9/L
  - Placebo (n=34): 44% (38.2% p<0.0001)
  - Avatrombopag (60 mg) (n=99): 68.9%
  - Avatrombopag (40 mg) (n=99): 88.1%

Adapt 2 (204 patients)

- Low Baseline Platelet Count Cohort: <40 x 10^9/L
  - Placebo (n=48): 48% (4.2% p<0.0001)
  - Avatrombopag (60 mg) (n=90): 68.9%
  - Avatrombopag (40 mg) (n=96): 88.1%

- High Baseline Platelet Count Cohort: 40 to <50 x 10^9/L
  - Placebo (n=34): 44% (20.6% p<0.0001)
  - Avatrombopag (60 mg) (n=99): 68.9%
  - Avatrombopag (40 mg) (n=99): 88.1%
Mean Platelet Counts by Treatment Group and Visit Day

Low Baseline Platelet Count Cohort:
- 60 mg Avatrombopag
- Placebo

High Baseline Platelet Count Cohort:
- 40 mg Avatrombopag
- Placebo

Baseline Procedure Day

Dosing:
- Visit 2 (Day 1) Baseline
- Visit 3 (Day 4) Dosing
- Visit 4 (Day 10) Procedure Day
- Visit 5 (Day 17)
- Visit 6 (Day 35)
## Combined Safety Data

<table>
<thead>
<tr>
<th>TEAEs, n (%)</th>
<th>Low Baseline Platelet Count Cohort &lt;40 x 10⁹/L</th>
<th>High Baseline Platelet Count Cohort 40 to &lt;50 x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=91) %</td>
<td>Avatrombopag 60 mg (n=159) %</td>
<td>Placebo (n=65) %</td>
</tr>
<tr>
<td>TEAEs, n (%)</td>
<td>53 (58.2)</td>
<td>89 (56.0)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>8 (8.8)</td>
<td>18 (11.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (6.6)</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (7.7)</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (7.7)</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (4.4)</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (4.4)</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>
Lusutrombopag Study Design

- Phase 3, multinational, randomized, double-blind, placebo-controlled study
  - Conducted at 138 study sites in 22 countries
- Platelet transfusion was required by the protocol if a patient’s post treatment pre-procedural platelet count was below $50 \times 10^9/L$

Screening (0 - 4 weeks) → Treatment period* (up to 7 days) → Post-treatment period (28 days)

<table>
<thead>
<tr>
<th>ICF</th>
<th>Randomization</th>
<th>LUSU (3 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>108 pts</td>
<td>107 pts</td>
<td>PBO</td>
</tr>
</tbody>
</table>

ICF, informed consent form; LUSU, lusutrombopag; MRI, magnetic resonance imaging; PBO, placebo; US, ultrasonography.

*If a patient met the stopping criterion on Day 5, 6 and 7 (platelet count $\geq 50 \times 10^9/L$ with an increase of $\geq 20 \times 10^9/L$ from baseline), no additional dose of study drug was administered.

Endpoints

• Primary endpoint:
  – Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure

• Key secondary endpoints (prespecified in the SAP):
  – Proportion of patients who required no platelet transfusion during the study
  – Proportion of responders: patients who achieved a platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
  – Number of days during which the platelet count was $\geq 50 \times 10^9$/L
Lusutrombopag

No platelet transfusions or rescue therapy (%)

<table>
<thead>
<tr>
<th>Patient %</th>
<th>Placebo</th>
<th>Lusu</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>64.8</td>
<td></td>
</tr>
</tbody>
</table>

Platelet > 50K and increased > 20K (%)

<table>
<thead>
<tr>
<th>Patient %</th>
<th>Placebo</th>
<th>Lusu</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>64.8</td>
<td></td>
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Platelet Response (ITT Population)

LUSU: platelet count in patients who did not receive platelet transfusion.
PBO: platelet count in patients who received platelet transfusion.
<table>
<thead>
<tr>
<th></th>
<th>Lusutrombopag</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>47.7 %</td>
<td>48.6%</td>
</tr>
<tr>
<td>SAE</td>
<td>6.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Bleeding related TEAE</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>PVT</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

TEAE: Treatment Emergent Adverse Events  
SAE: Serious Adverse Events  
47 year old male with decompensated alcohol-related cirrhosis

- Discussed TPO receptor agonists as an alternative to platelet transfusion.
- Searched Package Insert for drug interactions and signature adverse events.
- Undergoes repeat EGD with banding. Platelet count doubles measured immediately prior to procedure.
  - 34 to 67
- Patient tolerated TPO receptor agonist and endoscopy.
- Additional EGD with banding recommended.
47 year old male with decompensated alcohol-related cirrhosis

**History of Present Illness – August 2018**

- Undergoes 3rd repeat EGD with banding. Platelet count doubles again.
  - Platelet increases from 31 to 59
- Additional EGD recommended in 3 months.
Conclusions

- Patients with cirrhosis often need multiple invasive procedures
- Thrombocytopenia is common in patients with cirrhosis
- Severe thrombocytopenia places patients at risk of bleeding with invasive procedures
- Use of platelet transfusion to mitigate the risk is cumbersome and can be associated with adverse events
- The use of TPO agonists significantly increases platelet counts and can avoid the need for platelet transfusion
Clinical Case Forum II: Current and Emerging Management Approaches for the Patient with Hepatorenal Syndrome

R. Todd Frederick, MD
Acute Kidney Injury (AKI) in Cirrhosis

- Traditional criteria (IAC criteria)\(^1\)
  - 50% increase in SCr over baseline
  - Cut-off value of SCr: 1.5 mg/dL
- New definition of AKI\(^2\)
  - ↑ in SCr ≥0.3 mg/dL within 48 hours or ↑ SCr ≥50% from baseline that is known or presumed to have occurred within the prior 7 days

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<thead>
<tr>
<th>Stage AKI(^1)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Increase in SCr &gt;2- to 3-fold from baseline</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Increase of SCr &gt;3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy</td>
</tr>
</tbody>
</table>

AKI in Cirrhosis: Differential Diagnosis

• Prerenal
  – Hypovolemia: diuretics, GI bleeding, diarrhea
  – Hepatorenal syndrome

• Acute tubular necrosis: shock, nephrotoxic drugs, other

• Nephrotoxicity: NSAIDs, Iodinated contrast, other

• Intrinsic renal disease (glomerulonephritis, interstitial nephritis)

• Obstructive

• Miscellaneous, unknown

AKI and Cirrhosis

- AKI diagnosed with AKIN criteria associated with increased mortality in patients with cirrhosis\(^1\)
- Progression through stages strongly correlates with increased mortality\(^2\)
- However, serum creatinine cutoff of 1.5 mg/dL is still prognostic\(^3\)
  - Identifies patients at increased risk of mortality
- New AKI-HRS criteria enable earlier treatment (by 4 days) at lower creatinine (1 mg/dL lower)\(^4\)
  - Baseline serum creatinine is a predictor of response to therapy

Prospective Studies in Nonselected Hospitalized Patients


### Probability of survival (%)

| No AKI (n = 198) | 191 | 182 | 172 |
| AKI-1 (n = 44)   | 41  | 39  | 37  |
| AKI-1 (n = 66)   | 57  | 48  | 40  |
| AKI-2 (n = 30)   | 18  | 11  | 11  |
| AKI-3 (n = 37)   | 18  | 12  | 10  |

### Mortality (%)

- **No AKI**
  - **Stage 1**: p < 0.0001
  - **Stage 2**: p < 0.001
  - **Stage 3**: p < 0.01
- **AKI-1** (n = 44)
  - **Stage 1**: n.s.
  - **Stage 2**: p < 0.01
  - **Stage 3**: n.s.
- **AKI-2** (n = 30)
  - **Stage 1**: n.s.
  - **Stage 2**: p < 0.01
  - **Stage 3**: n.s.
- **AKI-3** (n = 37)
  - **Stage 1**: n.s.
  - **Stage 2**: p < 0.01
  - **Stage 3**: n.s.

- **sCR <1.5 mg/dl**
- **sCR ≥1.5 mg/dl**
60-Year Old Woman with Decompensated Cirrhosis

- Alcoholic liver disease
- Listed for liver transplant
- History of ascites, HE, esophageal varices with prior bleeding
- Labs 12 weeks ago in clinic: Na 136, Cr 1.1, bilirubin 1.8, INR 1.3, MELD 13
- Admitted to the hospital with worsening confusion
Worsening ascites over the past 3 months despite sodium restriction and alcohol abstinence

Diuretics recently increased to furosemide 80 mg daily, spironolactone 200 mg daily

Now requiring therapeutic paracentesis every 2 weeks (last 5 days ago)

Takes lactulose and rifaximin for HE

Takes propranolol for prophylaxis of EVH
On admission she is awake but disoriented with + asterixis

Initial BP 102/54, HR 78, T 100.2, RR 18, SpO2 95% on ambient air

Exam shows a distended abdomen with erythema, warmth, and severe tenderness at previous paracentesis site

Labs now: Cr 1.7, INR 2, Bili 4.5, Na 131, Ascites WBC 345 (46% PMNs, ANC 159), Blood Cx pending; MELD-Na 28

Oliguric and UA shows: Na <10, no protein or RBC, Cx pend
Patient Case (cont.)

• AKI (AKIN Grade 1)
• HE (Grade 2)
• Abdominal wall cellulitis
• Acute decompensation of cirrhosis

- Labs now: Cr 1.7, INR 2, Bili 4.5, Na 131, Ascites WBC 345 (46% PMNs, ANC 159), Blood Cx pending; MELD-Na 28
- Oliguric and UA shows: Na <10, no protein or RBC, Cx pend
Patient Case (cont.)

- Doppler US of abdomen shows moderate ascites, no liver masses, no hydronephrosis, no flow in portal vein visible
- Repeat BP is 88/52, HR 108
- Started on IV vancomycin and piperacillin/tazobactam
- IV albumin infused (1 gm/kg)
- Furosemide, spironolactone, and propranolol are discontinued
- Lactulose and rifaximin are continued

60-Year Old Woman with Decompensated Cirrhosis
Patient Case (cont.): Urine Output

Volume Intake/Output

-2000
-1500
-1000
-500
0
500
1000
1500
2000

Volume mL

Time, Days

IV Albumin

output intake

1 2 3 4 5
Hepatorenal Syndrome
International Ascites Club – Diagnostic Criteria

• Diagnosis of cirrhosis and ascites (portal hypertension)
• Meet AKI criteria
• No response after 2 days with withdrawal of diuretics and volume expansion with albumin (0.5-1 g/kg/day with max of 100 g/day)
• Absence of shock and recent use of nephrotoxic drugs
• No parenchymal kidney disease
  – No proteinuria > 500 mg/day, no microhematuria (> 50 RBC) and/or abnormal renal ultrasound (“medical renal disease”)
Pathophysiology AKI-HRS

- Portal Hypertension
- Decreased effective arterial volume (splanchnic)
- Endogenous vasoconstrictors
- Superimposed inflammatory response (infection, other)
- Reduced cardiac reserve (cirrhotic cardiomyopathy)
- Overwhelmed renal compensatory mechanisms
- Abrupt decline in GFR

Initial Management

- Early identification
- Assess and treat bacterial infection
  - Blood, urine, ascitic fluid culture
- Avoid large-volume paracentesis
- Stop β-blockers
- Stop nephrotoxic medications: NSAIDs, diuretics
- Volume expansion

Patient Case (cont.): Renal Function

Serum Creatinine mg/dl

Time, Days

Albumin

AKI-HRS Confirmed
Patient Case (cont.): Renal Function

![Graph showing changes in serum creatinine and albumin levels over time, with injections of Octreotide/Midodrine.](image-url)
Patient Case (cont.)

- Progressive renal failure despite albumin, midodrine and octreotide; creatinine rises to 4.3mg/dL
- Oliguria worsens and anasarca and hypoxemia develop
- Hypotension worsens
- Moved to the ICU and started on norepinephrine infusion
- Urgent activation for liver transplantation
- Discussions regarding renal replacement therapy
Patient Case (cont.): Renal Function

Serum Creatinine mg/dl vs Time, Days

- Octreotide/Midodrine
- Norepinephrine

Time, Days: 1, 2, 3, 4, 5, 6, 7, 8, 9

Serum Creatinine mg/dl: 0, 1, 2, 3, 4, 5, 6

At day 3 and day 6, there are interventions with arrows indicating Octreotide/Midodrine and Norepinephrine respectively.
Pharmacologic Therapy for HRS

IV Albumin
- 0.5-1gm/kg (max 100gm/d) for resuscitation; then
- 25 to 50 g/day

Plus

Vasoconstrictors
- Midodrine (+/- octreotide)
- Norepinephrine
- Terlipressin

**Midodrine Plus Octreotide: Dosing**

**Midodrine**: initially 7.5 mg oral 3 times daily
- Titrate to maximum of 12.5 mg 3 times daily

**Octreotide**: 100 µg SC 3 times daily
- Maximum dose 200 µg SC 3 times daily
- Titrate to achieve increase of MAP by 15 mmHg

**Note this is off-label treatment for HRS but recommended by AASLD Practice Guidelines**
### Comparative Efficacy of Midodrine and Norepinephrine: Systematic Review and Network Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>Short-Term Mortality</th>
<th>Reversal of HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Quality of Evidence</td>
</tr>
<tr>
<td><strong>Efficacy vs Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midodrine + octreotide</td>
<td>0.61 (0.19, 1.93)</td>
<td>Low (network)</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>0.75 (0.32, 1.76)</td>
<td>Low (network)</td>
</tr>
<tr>
<td><strong>Efficacy vs Midodrine + Octreotide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>1.50 (0.60, 3.78)</td>
<td>Low (network)</td>
</tr>
</tbody>
</table>

Terlipressin and Albumin

- Vasopressin analogue
- Prodrug with longer half-life
- Selective V1a > V1b or V2 activity
- Splanchnic and portal vasoconstriction
- Requires IV Albumin for HRS treatment

**Diagnosis of HRS**

- Terlipressin bolus IV 1 mg every 4-6 hours or continuous IV infusion (2 to 12 mg/day)
- Albumin IV 1 g/kg
- Albumin 20 to 40 g/day
- Increase terlipressin dose if creatinine does not decrease by 25% on day 3

Improvement in Renal Function: TERLI vs MID/OCT


**Response to Treatment, %**

- **Terlipressin**
  - Complete/partial response: 70.4%
  - Complete response: 55.6%
  - 

- **Midodrine + Octreotide**
  - Complete/partial response: 28.6%
  - Complete response: 4.8%

**P-values**

- Terlipressin vs Midodrine + Octreotide: $P=0.01$
- Complete response vs Complete/partial response: $P<0.001$
Fig. 4. Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders. Abbreviation: N.S., nonsignificant.
Systematic Review with Meta-Analysis: Vasoactive Drugs for the Reversal of HRS Type 1

# Safety: Terlipressin and Albumin

## Adverse Cardiovascular Effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>Terli+Alb n (%)</th>
<th>Albumin n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Circulatory overload</td>
<td>7 (30)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Suspected intestinal ischemia</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Not statistically significantly different

---


EASL website. Hepatorenal Syndrome.
Survival: Terlipressin and Albumin – ACLF

- Cumulative mortality at 90-days according to ACLF grade in responders and nonresponders to terlipressin and albumin
  - Baseline SCr and ACLF grade independently associated with response
  - Patient age, WBC, ACLF grade, and no response to treatment associated with mortality

RCT (Open Label): Terlipressin vs Norepinephrine in Patients with ACLF and HRS-AKI

- Continuous IV infusion of terlipressin (2 to 12 mg/day) vs. norepinephrine (0.5 to 3 mg/hour)

<table>
<thead>
<tr>
<th>Response Rate, n/N (%)</th>
<th>Norepinephrine</th>
<th>Terlipressin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>7/60 (11.7%)</td>
<td>16/60 (26.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 7</td>
<td>12/60 (20%)</td>
<td>25/60 (41.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Reversal of HRS-AKI</td>
<td>10/60 (16.7%)</td>
<td>24/60 (40%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- Terlipressin reduced need for RRT
- Terlipressin improved survival

Renal Function Predicts Post-LT Outcomes

- UNOS Database
- GFR < 40 predicted worse graft and patient survival post liver transplant

Treatment of HRS Pre-LT

- Successful reversal of HRS may improve post-LT outcomes

![Graph showing survival rates with patients at risk for HRS-treated and No-HRS groups over 3 years.](image)

Hepatorenal Syndrome

- Devastating complication of cirrhosis and ACLF
- Early recognition essential to improve outcomes; new diagnostic criteria offer promise
- Currently available treatment in the US has limited efficacy
- Terlipressin may be superior to other vasoconstrictors in reversing HRS
- In suitable patients, liver transplantation is the best treatment option
- Improving renal function reduces short-term mortality and need for RRT and may improve post-liver transplant outcomes
Clinical Case Forum III: Current Management Approaches for the Patient with Hepatic Encephalopathy

Steven L. Flamm, MD, FAASLD
Patient Case

HPI
- History of NASH and noted cirrhosis based on abdominal US about 4 years ago
- Noted melena one day prior to and hematemesis on the day of admission
- Her husband noted that she became confused on the way to the Emergency Unit and became unresponsive at the hospital

Social History
- Used to drink heavily as an bartender when she was young
- Quit drinking and smoking for the last 12 years
- Lives with husband

56-yr-old woman admitted for OHE for the first time
Patient Case (cont.)

56-yr-old woman admitted for OHE for the first time

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

**LABS**

- **BP**: 108/54 mm Hg
- **PR**: 116/min
- **RR**: 16/min
- **BMI**: 35 kg/m²
Patient Case (cont.)

56-yr-old woman admitted for OHE for the first time

- Lisinopril
- Metformin
- Simvastatin
- Baby aspirin
56-yr-old woman admitted for OHE for the first time

### Patient Case (cont.)

#### MEDICATIONS

#### HISTORY

#### LABS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/H</td>
<td>8.9/28</td>
</tr>
<tr>
<td>Platelets</td>
<td>79,000</td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
</tr>
<tr>
<td>Ammonia level</td>
<td>108</td>
</tr>
<tr>
<td>BUN</td>
<td>30</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.4</td>
</tr>
<tr>
<td>Na</td>
<td>132</td>
</tr>
<tr>
<td>K</td>
<td>3.2</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.1</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>45/32</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.2</td>
</tr>
<tr>
<td>Alk phos</td>
<td>122</td>
</tr>
<tr>
<td>MELD</td>
<td>19</td>
</tr>
</tbody>
</table>
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.

“Covert” HE Stages

Normal

“Overt” HE Stages

I  II  III  IV coma

Clinical Diagnosis

Worsening cognitive dysfunction

Role of Ammonia Testing in HE

“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)”
US Hospital Discharges Due to Cirrhosis Are Increasing

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.
Resource Utilization for Patients Hospitalized with Hepatic Encephalopathy, 2005-2009

Health Care Resource Utilization in Patients Discharged with HE Diagnosis

Average hospitalization charges

Number of procedures

Patient Case

How do you manage this patient?
Specific Approach to Overt HE Treatment

- Four-pronged approach to management of HE (GRADE II-2, A, 1):
  - Initiation of care for patients with altered consciousness
  - Alternative causes of AMS should be sought and treated
    - e.g. diabetic ketoacidosis, drugs (benzodiazepines, neuroleptics, opioids), neuroinfections, electrolyte disorders, intracranial bleeding and stroke
  - Identification of precipitating factors and their correction
  - Commencement of empirical HE treatment
# Current Therapy Options for HE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose(^1)</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>Rifaximin(^2)</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>Neomycin(^3)</td>
<td>Aminoglycoside antibiotic</td>
<td>Not to be used, renal and ototoxic risk</td>
</tr>
<tr>
<td>Metronidazole(^1)</td>
<td>Synthetic antiprotozoal and antibacterial agent</td>
<td>Not approved for HE</td>
</tr>
<tr>
<td>Vancomycin(^1)</td>
<td>Aminoglycoside antibiotic</td>
<td>Not approved for HE</td>
</tr>
</tbody>
</table>

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) P<0.001

58% relative reduction in the risk of a breakthrough episode

*Rifaximin 550 mg or placebo twice daily. 91% of patients in both arms received concomitant lactulose.
Rifaximin Randomized, Controlled Trial: Time to First HE-Related Hospitalization (Secondary Endpoint)

Hazard ratio with rifaximin, 0.50 (95% Cl, 0.29-0.87) 

P = .01

Placebo (77.4%) 

Rifaximin (86.4%)

50% relative reduction in the risk of HE-related hospitalization

56-yr-old woman admitted for OHE for the first time

Hospital Course

- She has an 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
  - Her husband was instructed to follow up in one week after discharge
Prevention of Overt HE (OHE)

- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)
Patient Case (cont.)

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

- Patients responding yes, %
  - 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

Patient Case (cont.)

Hospital Course

• She was re-admitted 9 days later due to recurrent grade III encephalopathy without melena

• She is taking lactulose only since unable to obtain rifaximin after discharge due to high co-pay
  – She has not seen her PCP yet
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

N=8,125 alive at discharge


- Patients (%)
  - 30 days: All-cause 27.4, HE-related 17.6
  - 180 days: All-cause 49.7, HE-related 33.7
  - 1 year: All-cause 56.4, HE-related 39.5

0 10 20 30 40 50 60

N=8,125 alive at discharge
### 30-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>1.28 (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>Hepatic encephalopathy</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>
## Unadjusted and Adjusted Odds Ratios for 90-Day Readmissions by Condition for Complications of Liver Disease

### 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><strong>2.44 (2.28-2.60)</strong></td>
<td><strong>2.53 (2.37-2.70)</strong></td>
<td><strong>3.07 (2.86-3.30)</strong></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>

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

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></th>
<th>Electronic</th>
<th>Checklist</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td>n=146</td>
<td>n=139</td>
<td>n=194</td>
</tr>
<tr>
<td>HE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic ascites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentage

Patient Case (cont.)

Discharge

- Follow up visit scheduled with gastroenterologist in 6 days
- 14 days of rifaximin obtained

56-yr-old woman admitted for OHE for the first time
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
  – To avoid the “revolving door”, treat after discharge

• Lactulose and rifaximin are important for secondary prophylaxis
Panel Discussion / Q&A