Hot Topics in Cirrhosis: A CASE-BASED APPROACH TO Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS)

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Salon F

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Hot Topics in Cirrhosis:
A CASE-BASED APPROACH TO
Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS)

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Breaking News

Kimberly Brown, MD
Henry Ford Hospital
Detroit, Michigan
New Evidence Confirms the Positive Impact of Antiviral Therapy for Hepatitis C on Outcomes
Antiviral Treatment Status and Risk of Renal and Cardiovascular Outcomes in Patients with Chronic Hepatitis C

- Chronic Hepatitis Cohort Study (CHeCS)
- Analyze the effect of sustained virologic response (SVR) (interferon [IFN]-based and direct-acting antiviral [DAA] therapy) and treatment failure on risk of acute coronary syndrome (ACS), end stage renal disease (ESRD) and ischemic stroke compared with untreated patients
- 15,999 chronic hepatitis C patients
  - 6,971 untreated, 4,853 treated with DAAs and 3,467 treated with IFN-based regimen

SVR was associated with reduced risk of ACS, ESRD and ischemic stroke, regardless of treatment type (P ≤ 0.0001 for all)

- Effects of DAA SVR and IFN SVR similar for both ACS (sHR 0.64 and 0.62 for DAA and IFN, respectively) and ESRD (sHR = 0.62 and 0.50)

- Effects of DAA SVR was associated with a significantly lower risk of ischemic stroke than IFN SVR (sHR = 0.39 vs 0.68, respectively)
DAA Regimens Are Associated with Significant Reduction in LR Mortality (ERCHIVES)

- Excluded those with HIV or HBV coinfection and those with HCC
- Used propensity matched untreated controls
- Liver-related (LR) death
  - Included viral hepatitis related causes, complications of liver disease and HCC
  - Excluded any cause where alcohol or any other known liver disease other than viral hepatitis was specified
- Overall LR mortality rate per 100 person-years (PY) of follow up was 0.68 in the treated and 1.29 in the untreated group (P<0.0001)
  - Among treated, LR mortality rate per 100 PY was 0.14 for those who achieved SVR vs 1.4 among those who did not
  - Reduction largely driven by attainment of higher SVR among DAA-treated persons

# Liver Related Mortality Rate per 100 PY of Follow Up

<table>
<thead>
<tr>
<th></th>
<th>Liver-related deaths</th>
<th>Non-liver-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate/100PY (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A: HCV+ treated</td>
<td>1057</td>
<td>0.68 (0.64, 0.72)</td>
</tr>
<tr>
<td>Group B: HCV+ untreated</td>
<td>1921</td>
<td>1.29 (1.23, 1.35)</td>
</tr>
<tr>
<td><strong>Among those treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By treatment response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR achieved</td>
<td>127</td>
<td>0.14 (0.12, 0.17)</td>
</tr>
<tr>
<td>SVR not achieved</td>
<td>930</td>
<td>1.40 (1.31, 1.49)</td>
</tr>
<tr>
<td>By treatment regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG/RBV</td>
<td>963</td>
<td>0.76 (0.72, 0.81)</td>
</tr>
<tr>
<td>DAA</td>
<td>73</td>
<td>0.31 (0.24, 0.38)</td>
</tr>
<tr>
<td>By treatment regimen and SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG/RBV SVR achieved</td>
<td>84</td>
<td>0.13 (0.1, 0.16)</td>
</tr>
<tr>
<td>PEG/RBV SVR not achieved</td>
<td>879</td>
<td>1.44 (1.35, 1.54)</td>
</tr>
<tr>
<td>DAA SVR achieved</td>
<td>40</td>
<td>0.20 (0.14, 0.27)</td>
</tr>
<tr>
<td>DAA SVR not achieved</td>
<td>33</td>
<td>0.81 (0.54, 1.09)</td>
</tr>
</tbody>
</table>

HCV Cure Improves 5-Year Overall and LR Survival in HCV-Related HCC Patients

- Mono-infected HCV-related HCC patients at 2 US and 6 Asian centers between 2005-2017
- Propensity score matching lead to 321 patients untreated vs 321 patients with SVR
- All received HCC treatment
- SVR patients had higher 5 year OS
- Analysis at 90, 180 and 360 days also showed SVR was independently associated with lower risk of death
- HCV-related HCC patients who are candidates for HCC therapy should also be considered for DAA therapy

Summary

• These data support prior studies showing that SVR in patients treated with DAAs for Hepatitis C is associated with
  – Reduction in liver related mortality
  – Reduction in risk of cardiovascular and renal disease
  – Improved 5 year survival in HCV-related HCC patients
New Evidence Supports Possible Expanded Use of Rifaximin in Patients with Cirrhosis
Rifaximin for the Prevention of HE in Patients Treated by TIPS

- Rifaximin (600 mg BID) vs placebo in 186 patients treated by TIPS
- Treated 15 days before TIPS and for 6 months after procedure
- Indications for TIPS: Recurrent ascites (86%) and prevention of rebleeding (16%)
- Mean MELD was 11.9 +/- 3.9 and Child Pugh was 8.1 +/- 1.1
- 20% had prior HE episode

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month probability of free from HE</td>
<td>59.1%</td>
<td>44.2%</td>
<td>P=0.05</td>
</tr>
<tr>
<td>Transplant free survival at 6 months</td>
<td>93.2%</td>
<td>84.0%</td>
<td>P=0.05</td>
</tr>
</tbody>
</table>

Impact of GI Consultation and Medical Therapy on Clinical Outcomes

- 186,160 Medicare-enrollees with cirrhosis followed for 4.57 years
- 49% had NAFLD cirrhosis
- 31% were evaluated by a GE
- Overall survival at 2 years: 45.6% (95%CI[45.1, 46.1])
- NAFLD posed highest adjusted risk of death (HR 1.07, 95% CI (1.02-1.12))

Survival of HE Patients: Age 65 and Over

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Number of Patients at Risk</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>28013</td>
</tr>
<tr>
<td>1</td>
<td>14641</td>
</tr>
<tr>
<td>2</td>
<td>9522</td>
</tr>
<tr>
<td>3</td>
<td>6158</td>
</tr>
<tr>
<td>4</td>
<td>3716</td>
</tr>
<tr>
<td>5</td>
<td>1886</td>
</tr>
</tbody>
</table>

Strata
- Patients under Age of 65
- Patients over Age of 65

Survival probability over time.
Impact of GI Consultation and Medical Therapy on Clinical Outcomes

- Both GE consultation and rifaximin utilization were associated with lower mortality, respective adjusted HR [0.73 95%CI (0.67, 0.80)] and [0.40 95%CI (0.39-0.42)]
- 30-day readmissions fewer for patients seen by GE [0.71 95%CI (0.57, 0.88)] and taking rifaximin [0.18 95%CI (0.08, 0.40)]
- Many patients did not receive HE-therapy after discharge from an HE-hospitalization
- Optimal therapy (fewer hospital days), compared to no therapy, was combination of lactulose and rifaximin, IRR 0.28 95% CI (0.27-0.30)
- Care coordination efforts critical for persons with cirrhosis

Tapper EB et al. The Liver Meeting, Boston, MA 2019, Abstract 121.
Summary

• These data suggest the use of rifaximin reduces the risk of HE in patients undergoing TIPS.
• In addition, the use of rifaximin (perhaps through consultation with GE) may be associated with improved overall mortality and a reduction in readmissions.
New Therapy for Pruritus in Patients with Primary Sclerosing Cholangitis (PSC) or Primary Biliary Cholangitis (PBC)
Bezafibrate Improves Pruritus in PSC/PBC

- Bezafibrate (PPAR agonist) 400 mg QD vs PBO for 21 days
- 70 PSC, PBC or SSC patients with pruritus (baseline itch intensity of at least 5 out of 10 on VAS)
- Significant decreases in alkaline phosphatase (ALP) (36% on bezafibrate vs 0% on PBO; p=0.04)

Interim Analysis Finds Obeticholic Acid (OCA) to be Associated with Positive Endpoints in Patients with NASH
Secondary Analyses in Patients with NASH Across Fibrosis Scores

- Diabetes, hypertension and elevated transaminases are drivers of fibrosis progression in patients with NASH
- 1:1:1 randomization (Placebo, 10 mg obeticholic acid or 25 mg obeticholic acid QD) (n=1218)
- 18-month interim analysis
- Patient population:
  - NASH with F1 and ≥1 Risk Factor (BMI >30 kg/m², T2DM, ALT ≥1.5 ULN)
  - NASH with F2 or F3 fibrosis

Sanyal AJ et al. The Liver Meeting, Boston, MA 2019, Abstract 34.
Secondary Analyses in Patients with NASH Across Fibrosis Scores

- **Patient population**
  - 24% F1 + Risk Factor
  - 76% F2 or F3
- **Results consistent with previously reported primary efficacy analysis of F2/F3 patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>OCA 10 mg</th>
<th>OCA 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Efficacy Population (F1-F3)</strong></td>
<td>n=407</td>
<td>n=407</td>
<td>n=404</td>
</tr>
<tr>
<td>Fibrosis improvement + no worsening of NASH</td>
<td>10.6%</td>
<td>15.7%</td>
<td>21.0%</td>
</tr>
<tr>
<td></td>
<td>p=0.029</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NASH resolution + no worsening of fibrosis</td>
<td>7.9%</td>
<td>11.3%</td>
<td>14.9%</td>
</tr>
<tr>
<td></td>
<td>p=0.09</td>
<td>p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

Sanyal AJ et al. The Liver Meeting, Boston, MA 2019, Abstract 34.
Summary

• These data support the positive impact of OCA in patients with NASH across fibrosis scores F1-F3.
HRS-AKI: A Medical Emergency

Hugo E. Vargas, MD
Professor of Medicine
Mayo Clinic Arizona
Rick
38 yo Man With A1ATD, Decompensated Cirrhosis

• A1ATD liver disease
• Listed for liver transplant
• History of ascites, HE, esophageal varices with prior bleeding
• Labs 12 weeks ago in clinic: Na 136, Cr 1.3, bilirubin 2.0, INR 1.30, MELD$_{NA}$ 15
• Admitted to the hospital with worsening confusion
Rick
38 yo Man With A1ATD, Decompensated Cirrhosis

• Worsening ascites over the past 3 months despite sodium restriction
• Diuretics recently increased to furosemide 80 mg daily, spironolactone 100 mg daily
• Now requiring therapeutic paracentesis every week (last 5 days ago)
• Takes lactulose and rifaximin for HE
Rick
38 yo Man With A1ATD, Decompensated Cirrhosis

- On admission he is awake but disoriented with + asterixis
- Initial BP 102/54, HR 78, T 37.7C, RR 18, SpO2 95% on ambient air
- Exam shows a distended abdomen, mild tenderness to palpation
- Labs now: Cr 1.70, INR 2, Bili 4.5, Na 130, Ascites WBC 500 (76% PMNs), Blood Cx pending; MELD-Na 30
- Oliguric and UA shows: Na <10, no protein or RBC, Cx pend
ARS Question

Based on the presentation what is the most appropriate clinical plan?

A. Begin IV ceftriaxone empirically
B. Begin IV ceftriaxone and aggressive hydration with NS
C. Await culture results and replenish intravascular space with albumin
D. Begin IV ceftriaxone empirically and replenish intravascular space with albumin

Answer is D
Acute Kidney Injury (AKI) in Cirrhosis

- **Traditional criteria (International Club of Ascites 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

<table>
<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
- Intrinsic renal disease (glomerulonephritis, interstitial nephritis)
- Obstructive
Rick
38 yo Man with A1ATD, Decompensated Cirrhosis

- On admission he is awake but disoriented with + asterixis
- Initial BP 102/54, HR 78, T 37.7°C, RR 18, SpO2 95% on ambient air
- Exam shows a distended abdomen, mild tenderness to palpation
- Labs now: Cr 1.70, INR 2, Bili 4.5, Na 130, Ascites WBC 500 (76% PMNs), Blood Cx pending; MELD-Na 30
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On admission he is awake but disoriented with + asterixis

Initial BP 102/54, HR 78, T 37.7C, RR 18, SpO2 95% on ambient air

Exam shows a distended abdomen, mild tenderness to palpation

Labs now: Cr 1.70, INR 2, Bili 4.5, Na 130, Ascites WBC 500 (76% PMNs), ESR 110

Oliguric and UA shows: Na <10, no protein or RBC, Cx pending

1. AKI (Stage 1b)
2. Hepatic Encephalopathy (Stage 2)
3. Spontaneous Bacterial Peritonitis
4. Acute on Chronic Liver Failure (renal, CNS and infection)
Doppler US of abdomen shows moderate ascites, no liver masses, no hydronephrosis

Repeat BP is 88/52, HR 108

Started on IV ceftriaxone

IV albumin infused (1 gm/kg)

Furosemide, spironolactone, and propranolol are discontinued

Lactulose and rifaximin are continued
Prevention of HRS in Patients with Cirrhosis

• Avoid NSAIDs
• Avoid ACE inhibitors
• Decrease/withdraw diuretics when decompensated
• Consider lactulose and volume of stool output
• Threshold at which to discontinue beta-blockers?
• Maintain mean arterial pressure (MAP)
  – No good data on prevention, but an increase with successful treatment is common
  – Data suggest that those with lowest MAP may respond to medical treatment best
Albumin

- 50% of plasma proteins
  - Liver produces it, 10-15 g/day
  - 30%-40% remains in the intravascular space

- Structurally:
  - 67 kDa in size, 609 amino acids
  - Charge is net negative (pH 7)
  - Circulates in net reduced form
  - Albumin has heart-shaped tertiary structure with high α-helical content

Albumin: Role in the Treatment of Cirrhosis and Its Complications

**Capillary permeability**
- Oncotic Pressure
- Hemostatic effect
- Endothelial stabilization
- Antioxidant
- Immuno-modulation

**Albumin functions**

- **Oncotic Pressure**
  - \(-\)ve charge
  - High concentration
  - Intravascular distribution

- **Capillary permeability**
  - \(-\)ve charge
  - Extracellular distribution

- **Hemostatic effect**
  - Cys-34
  - High Concentration

- **Endothelial stabilization**
  - Endotoxin binding inactivation
  - ↑ Intracellular glutathione
  - ↓ TNF-induced NF-κB activation
  - Intracellular distribution

- **Antioxidant**
  - Cys-34
  - N terminal: Metal binding
  - Bilirubin binding

- **Immuno-modulation**
  - Endotoxin binding inactivation
  - ↑ Intracellular glutathione
  - ↓ TNF-induced NF-κB activation

Rick: Update

- Progressive renal failure despite albumin, creatinine rises to 3.33 mg/dL
- Oliguria and anasarca worsens
- Hypotension worsens
- MELD upgraded
- Discussions regarding renal replacement therapy
ARS Question

What do you consider the most appropriate plan at this juncture?

A. Transfer to ICU, begin dopamine
B. Begin midodrine 5mg TID, octreotide 200 µg SC TID
C. Continue IV albumin 40-60 g/24h
D. Continue IV albumin 40-60 g/24h, introduce terlipressin

Answer is D
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**

Terlipressin vs Midodrine/Octreotide: Improvement in Renal Function


- **Response to Treatment, %**
  - **Complete/partial response**
    - Terlipressin: 70.4%
    - Midodrine + Octreotide: 28.6%
  - **Complete response**
    - Terlipressin: 55.6%
    - Midodrine + Octreotide: 4.8%

- **Statistical Significance**
  - *P*=0.01
  - *P*<0.001
Terlipressin vs Midodrine/Octreotide: 90-Day Survival

Probability of 90-Day, Transplant-Free Survival According to Response to Treatment

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.

Terlipressin + Albumin vs Albumin Alone for HRS-1 (CONFIRM Study)

- Randomized, placebo-controlled study in 300 patients
- 2:1 to terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups
- Treatment for 14 days unless one of the following occurred:
  - Verified HRS reversal (VHRSR) (decrease in SCr to ≤1.5 mg/dL)
  - Renal replacement therapy (RRT)
  - Liver transplantation (LT) or
  - SCr at or above baseline (BL) at Day 4
- Primary Endpoint
  - VHRSR defined as 2 consecutive SCr values ≤1.5 mg/dL, at least 2 hours apart, with patient alive without RRT for ≥10 days after the second SCr ≤1.5 mg/dL

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)

- **Terlipressin (N=199):** 29.1%
- **Placebo (N=101):** 15.8%

\[ P = 0.012 \]

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)

- **Terlipressin (N=199)**: 31.7% (n=63)
- **Placebo (N=101)**: 15.8% (n=16)

**P=0.003**

- **From a CMH Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L).**
- **Percentage of subjects with HRS reversal without RRT to day 30.**

## Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

<table>
<thead>
<tr>
<th>Preferred Terma</th>
<th>Terlipressin (N=200)b % (n)</th>
<th>Placebo (N=99)b % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>19.5 (39)</td>
<td>6.1 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16.0 (32)</td>
<td>10.1 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.0 (26)</td>
<td>7.1 (7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12.5 (25)</td>
<td>5.1 (5)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>10.5 (21)</td>
<td>5.1 (5)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>10.0 (20)</td>
<td>13.1 (13)</td>
</tr>
</tbody>
</table>

Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial; REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

AEs, adverse events; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group.
aUp to 7 days posttreatment. bSubjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.

Rick’s Renal Function

Creatinine mg/dL

<table>
<thead>
<tr>
<th>Hospital days</th>
<th>Creatinine mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.67</td>
</tr>
<tr>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>3.33</td>
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<tr>
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</table>

- TERLIPRESSIN 1mg IV q6
- Albumin 1g/kg
AKI in Cirrhosis: When is it HRS?

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to International Club of Ascites – AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight, 100g max)
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury defined as:
  - Absence of proteinuria (>500 mg/day)
  - Absence of microhaematuria (>50 RBCs/hpf)
  - Normal findings on renal ultrasonography

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

Pathophysiology AKI-HRS

Take Home Points

• AKI in chronic liver disease impacts mortality
• HRS is defined as AKI that does not respond to volume resuscitation upon correction of sepsis and in the absence of other renotoxic insult
• Current classification expedites the recognition of HRS-AKI and allows for potential intervention
• Vasoactive agents (terlipressin and norepinephrine) can reverse HRS-AKI in a percentage of patients
• Terlipressin is superior to other agents in reversing HRS with expected survival benefits
  – Phase 3 CONFIRM US study results now available
Hot Topics in Cirrhosis: A CASE-BASED APPROACH TO Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS)

HRS-CKD: A Slippery Slope

Robert S. Brown, Jr., MD, MPH
Gladys and Roland Professor of Medicine
Vice Chair, Mentorship and Academic Development
Clinical Chief, Division of Gastroenterology & Hepatology
Luis
65-Year-Old Man with NASH/EtOH Cirrhosis

History

• Long history of EtOH (3-4/day) and T2DM
• Diagnosed with cirrhosis 2 years ago in evaluation for low platelets, stopped drinking
• Baseline SCr = 1.1 mg/dL 1 month ago
• Bilirubin 0.9, INR 1.1, albumin 2.7
• On aldactone 150 QD, Lasix 30 BID, metformin and carvedilol for EV on endoscopy
Luis is Hospitalized

- Admitted for tense ascites
- Hyponatremia, Na 127
- Admission paracentesis: PMN cell count = 200/mm³
- SCr = 1.45 mg/dL
- MELD 11
- MELD_{NA} 20
- MAP = 60 mmHg
SCr is an Independent Predictor of Mortality in Patients with Cirrhosis

Any increment increase in SCr within 48 hours from hospitalization is associated with a higher mortality, provided the peak SCr within 48 hours is $>1.2 \text{ mg/dL}$.

Serum creatinine of 1.5 g/dL corresponds to GFR of ~30 mL/min

a. Inker LA, Perrone R. UpToDate.
ARS Question

Initial treatment should include:
A. IV albumin 50 g × 2 days
B. Ceftriaxone 1 g IV QD x 5 days
C. Increase diuretics
D. LVP 1-4 L
E. A and D

Correct answer is E
Luis’ Hospital Course

- Diuretics held
- Una < 10 mEQ/L
- U/A (-) sediment
- Undergoes 4 L LVP with 25% albumin
- Creat decreases to 1.15, Na increases to 132
What Next for Luis?

- Restart diuretics? Dose?
- Fluid restrict? How much?
- Serial paracenteses?
- TIPS?
- Does he need transplant evaluation?
Prognosis of Patients with Cirrhosis at Onset of Ascites

Patients With Refractory Ascites Have a Worse Survival Than Patients with Diuretic-Responsive Ascites

Survival probability

Refractory ascites

Non refractory ascites

p<0.001

Months

Survival probability

0.0
0.2
0.4
0.6
0.8
1.0

0 12 24 36 48 60 72 84

Luis Is Discharged

- Discharged home on aldactone 50 QD and Lasix 20 QD
- 2 weeks later fluid has reaccumulated
- Diuretics increased
- Returns to clinic with tense ascites
ARS Question

What now?
A. Midodrine + octreotide + albumin
B. Discontinue beta blocker
C. Fluid restrict to 1.5 L
D. Serial paracenteses
E. TIPS

Answer: Can be multiple options but this is to get a sense of audience preference
Update on Luis

• Undergoes LVP with albumin
• Beta blocker discontinued
• 1 week later SCR is 1.57 and Na now 125
• Admitted for urgent OLT eval and IV albumin
• Tap (-) SBP
• Diuretics held
HRS Type 1 and 2

New Nomenclature

Type 1
HRS → HRS-AKI

Type 2
HRS → HRS-CKD
Survival in Patients with Ascites and HRS

Case Conclusion for Luis

- Undergoes TIPS
- Listed for OLT but at low MELD
- Scr remains at 1.2
- Develops recurrent HE requiring lactulose and rifaximin
- Low MELD with little access to OLT
- Would there have been an alternate Rx for HRS CKD?
Probability of survival without liver transplantation in patients allocated to covered TIPS group and in those allocated to LVP+A group.

TIPS: Patient Selection

Platelet count >75 and serum bilirubin <2.9 mg/dL

Platelet count <75 and serum bilirubin >2.9 mg/dL

Survival

Month

0.0 0.2 0.4 0.6 0.8 1.0

0 2 4 6 8 10 12

Evaluating AKI in Cirrhosis: What Do I Do?

R. Todd Frederick, MD
Fellowship Director
Hepatology and Liver Transplant
California Pacific Medical Center
Larry

- 59 yo M w/ decompensated cirrhosis (ALD) presents with 3 weeks of worsening leg and abdominal swelling
- Recently injured his back helping his neighbor move
- He escalated his furosemide to 80 mg BID but doesn’t feel its working
- Denies fever, jaundice, confusion, bleeding

PMHx: ALD, cirrhosis, ascites, HE, bleeding EV s/p banding, gout, depression

Social Hx: no recent EtOH, lives with roommate, unable to work for last 3 years

Meds: furosemide, spironolactone, allopurinol, escitalopram, lactulose
Larry’s Evaluation

- BP 115/70, HR 88, RR 16, afebrile
- Chronically ill appearing, muscle wasting, gynecomastia
- Oriented without asterixis
- Cardiac – normal, no JVD
- Reduced BS at right base
- Large ascites, splenomegaly, no TTP
- No CVA tenderness
- Moderate pitting edema in legs

T. Bili 1.9, INR 1.6  
WBC 2.3, Hgb 8.9  
Na 130, Creat 2.6 (1.2 two weeks ago)  
MELD-Na 27  
U/A: 1.009/WBC neg/RBC few/+cellular casts (mod)  
Urine Na 46, Fe Urea 48%, Ur Osm 310

Abd US: small cirrhotic liver w/o mass, no biliary dilation, enlarged spleen, patent PV, large ascites, normal appearing kidneys

CXR – moderate right pleural effusion
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Oh no. This patient is sick. What do you think is going on? What do you do now?

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Larry – The Plot Thickens…

• You admit Larry to the hospital for AKI (Stage 2)
• Additional history obtained by your medical student:
  – Larry began taking ibuprofen for his severe back pain 3-4 weeks ago
ARS Question

Which of the following would be inappropriate at this time:

A. Start evaluation for liver transplant
B. Perform a diagnostic paracentesis
C. Give a trial of furosemide 100 mg IV to mobilize ascites and edema
D. Administer IV albumin at 1g/kg
E. Consult palliative care

Answer = (c) give a trial of furosemide
Larry – Conclusion

- Diagnosed with NSAID-induced AKI
- Resuscitated with albumin
- SBP excluded
- Approved for listing for liver transplant
- AKI recovered over the next several days
- Discharged home for ongoing care with instructions to avoid future NSAID use
Background: AKI in Cirrhosis

• A common and serious problem
  – ~20-50% of hospitalized cirrhotic patients
  – Increased risk of short-term mortality
• AKI – 3 general types:
  – (1) Pre-renal (includes HRS), “Functional”
  – (2) Intra-renal (ATN, GN, AIN), “Structural”
  – (3) Post-renal, “Obstructive”
• How to diagnose?
  – Careful history and physical exam
  – Fluid/Albumin challenge
  – U/A, Renal US, Urine Lytes, Urine Eos

<table>
<thead>
<tr>
<th>Stage AKI¹</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>

Hospitalized patients with cirrhosis

- Chronic renal failure 1%
- ARF / AKI 19% (293/154)

  - Pre-renal 68% (437/639)
    - Volume-responsive 66% (288/437)
      - Infection
      - Hypovolemia
      - Vasodilators
      - Other
    - Not volume-responsive
      - HRS Type 1 25% (108/437)
      - HRS Type 2 9% (41/437)
  - Intra-renal (ATN, GMN) 32% (224/712)
  - Post-renal (obstructive) (<1%)
# AKI in Cirrhosis – How to Differentiate?

<table>
<thead>
<tr>
<th></th>
<th>Pre-renal (non-HRS)</th>
<th>Intrarenal (ATN/other)</th>
<th>Hepatorenal (HRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Volume</td>
<td>Low (&lt;500ml)</td>
<td>Low to High</td>
<td>Low (&lt;500ml)</td>
</tr>
<tr>
<td>Urine Sodium</td>
<td>Low (&lt;20)</td>
<td>Moderate to High (&gt;40)</td>
<td>Low (&lt;20)</td>
</tr>
<tr>
<td>Response to Fluid?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urine Sp Gravity</td>
<td>&gt;1.020</td>
<td>≤1.010</td>
<td>&gt;1.020</td>
</tr>
<tr>
<td>FeNa*</td>
<td>&lt;1%</td>
<td>&gt;2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Fe Urea¹</td>
<td>&lt;35%</td>
<td>&gt;33%</td>
<td>&lt;33%</td>
</tr>
<tr>
<td>Urine Osm</td>
<td>&gt;500</td>
<td>&lt;350</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Urine Sediment</td>
<td>Bland/Normal, Few granular or hyaline casts</td>
<td>Cellular casts, “muddy brown” casts, RBC casts</td>
<td>Bland to few granular casts</td>
</tr>
<tr>
<td>BUN/Cr</td>
<td>&gt;20</td>
<td>&lt;15</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>None to trace</td>
<td>Mild to moderate</td>
<td>None to trace</td>
</tr>
<tr>
<td>Urine NGAL²</td>
<td>Low</td>
<td>High</td>
<td>Low-Moderate</td>
</tr>
</tbody>
</table>

*Additional clues for HRS: Cirrhosis with portal HTN, Ascites, Hyponatremia*

*Caution if taking diuretics; *NGAL, neutrophil gelatinase-associated lipocalin.

Cindy

- 66 yo F with NASH cirrhosis presents with weakness and confusion
- Husband noticed slurring of her words, unable to carry on a conversation
- Increased lactulose 2 weeks ago and now has a hard time leaving the house, soiling herself, >8 loose stools/day
- Denies fever, bleeding, vomiting

PMHx: NASH cirrhosis, ascites, HE, Diabetes, HTN, chronic cholecystitis, hyperlipidemia, obesity

Social Hx: Lives with husband, no EtOH/Tob/Drugs, no travel

Meds: furosemide, spironolactone, lactulose, atorvastatin, carvedilol, metformin
Cindy’s Evaluation

- BP 92/50, HR 108, RR 18, afebrile
- Chronically ill appearing with obesity but sarcopenia, scleral icterus, dry oral mucosa
- Disoriented with asterixis, otherwise nonfocal exam
- Tachycardic, no JVD; lungs clear
- No ascites, + splenomegaly, firm nontender liver in epigastrium
- Spider angiomata and jaundice
- No edema

T. Bili 4.9, INR 1.9
WBC 4.3, Hgb 11, Plt 34
Na 147, Creat 3.6 (1.1 three weeks ago)
MELD-Na 32
U/A: 1.030/WBC many/RBC rare/+few granular casts
Urine Na 24, Fe Urea 28%, Ur Osm 520

Abd US: cirrhotic liver, no biliary dilation, +GS in GB with thick wall, enlarged spleen, patent dilated PV, trace ascites, normal kidneys

CXR – clear
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Oh no, another very sick patient! What do you think is going on? What do you do now?
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CXR – clear
Cindy Goes to the Hospital

- You admit her to the hospital for AKI (Stage 3) and acute on chronic liver failure (ACLF)
- You administer IVF (saline) and albumin 1 gm/kg/d
- You hold her diuretics
- You stop her metformin
- You order blood and urine cultures
- You initiate a liver transplant evaluation
ARS Question

Which of the following is the next **most appropriate** step:
A. Obtain a head CT to r/o hemorrhage or stroke
B. Obtain an Abd CT to assess for acute cholecystitis
C. Start octreotide + midodrine for HRS
D. Stop carvedilol
E. Place her on a low protein diet to reduce her ammonia

**Answer = (d) Stop carvedilol**
Cindy – Conclusion

• UTI diagnosed and treated
• She responded to several days of resuscitation with normal saline and albumin, creatinine returned to 1.2
• Rifaximin was added to her regimen for recurrent HE; lactulose dosing was decreased
• She was asked to discuss management of her HTN with her cardiologist
• She is scheduled for a surveillance endoscopy
Hepatorenal Syndrome
International Ascites Club – Diagnostic Criteria

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

AKI – Initial Management

- Early identification
- Assess and treat bacterial infection
  - Blood, urine, ascitic fluid culture, CXR
- Assess and treat GI bleeding
- Avoid large-volume paracentesis (diagnostic OK)
- Stop β-blockers
- Stop nephrotoxic medications: NSAIDs, diuretics
- Volume expansion
  - Saline for those with definite or suspected volume depletion
  - Albumin for those with AKI Stage 1B or higher

Stage 1 AKI

Stage 2 and 3 AKI

Resolution → Stable → Progression

Close monitoring
Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, decrease/withdrawal of diuretics, treatment of infections when diagnosed), plasma volume expansion in case of hypovolemia

Withdrawal of diuretics (if not withdrawn already) and volume expansion with albumin (1 g/kg) for 2 days

Response

YES → NO

Meets criteria of HRS

NO → YES

Close follow up

Further treatment of AKI decided on a case-by-case basis

Specific treatment for other AKI phenotypes

Vasoconstrictors and albumin

Summary – AKI in Cirrhosis

- Early recognition and intervention is needed
- Consider the differential diagnosis of AKI
  - More than one cause may be evident
  - Management and prognosis vary depending on etiology
  - AKI-HRS remains a diagnosis of exclusion
- Not all AKI in cirrhosis is HRS
Panel Discussion/Q&A