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Recognizing and Managing Acute Kidney Injury and HRS

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Disclosures

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Speaker Bureau: Gilead Sciences, Clinical Area – HCV
Speaker Bureau: Intercept, Clinical Area – PBC
Consultant: Intercept Pharmaceuticals, Clinical Area – PBC
Consultant: AbbVie, Clinical Area – HCV
Defining Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS)
Revised HRS Definitions and Criteria: No Longer Type 1 and Type 2

<table>
<thead>
<tr>
<th>Old classification</th>
<th>New classification</th>
<th>Criteria</th>
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</thead>
</table>
| HRS-1*             | HRS-AKI            | a) Absolute increase in sCr ≥0.3 mg/dl within 48h and/or
|                    | (A Medical Emergency) | b) Urinary output ≤0.5 ml/kg B.W. ≥6h* or
|                    |                    | c) Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value |
| HRS-2*             | HRS-NAKI           | a) eGFR <60 ml/min per 1.73 m² for <3 months in the absence of other (structural) causes
|                    | HRS-AKD            | b) Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value |
|                    | HRS-CKD            | c) eGFR <60 ml/min per 1.73 m² for ≥3 months in the absence of other (structural) causes |

International Club of Ascites Diagnostic Criteria for HRS-AKI

- Cirrhosis; acute liver failure; acute-on-chronic liver failure
- Increase in sCr, >0.3 mg/dL within 48 hours or >50% from baseline value and/or
- Urinary output < 0.5 ml/kg of body weight for > 6 hours (requires use of a urinary catheter)
- No full or partial response for >2 days of diuretic withdrawal and volume expansion with albumin (dosed at 1 g/kg of body weight/day*)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- In the absence of CKD, assess for parenchymal disease, as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography
- Suggestion of renal vasoconstriction, with FENa <0.2% (levels <0.1% are considered highly predictive)

*Maximum 100 g/day
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\(^2\)**
  - \(\uparrow\) in SCr \(\geq 0.3\) mg/dL within 48 hours or \(\uparrow\) SCr \(\geq 50\%\) 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 (\geq 0.3) mg/dL or an increase in SCr (\geq 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 (\geq 4.0) mg/dL with an acute increase (\geq 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

- **Intrinsic renal disease**
  - Acute tubular necrosis
  - Glomerulonephritis
  - Interstitial nephritis

- **Obstructive**
Prevalence and Etiology of AKI in Cirrhosis

Hospitalized patients with cirrhosis

Chronic renal failure 1%

ARF / AKI 19% (293/1544)

Pre-renal 68% (437/639)

Intra-renal (ATN, GMN) 32% (224/712)

Post-renal (obstructive) (<1%)

Volume-responsive 66% (288/437)
- Infection
- Hypovolemia
- Vasodilators
- Other

Not volume-responsive

HRS Type 1
25% (108/437)

HRS Type 2
9% (41/437)

HRS-AKI Management
Pharmacologic Therapy for AKI-HRS

IV Albumin

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

Plus

Vasoconstrictors

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

Midodrine and Octreotide

**Midodrine**
- Midodrine binds to alpha-1-adrenergic receptors
  - Improves systemic blood pressure and hence improves renal perfusion pressure
- Start at 7.5 mg TID
- Titrate midodrine up to 15 mg TID on consecutive doses to a mean arterial pressure of >80 mmHg

**Octreotide**
- Octreotide is a splanchnic vasoconstrictor that antagonizes the action of various splanchnic vasodilators
  - Not effective alone
- Start octreotide 100-200 mcg TID or IV infusion 50 mcg/hr to raise MAP by 15 mm Hg
- Maximum dose 200 mcg SC TID
Terlipressin: Under FDA Review in US*

- Approved in many ex-US countries for years
- Synthetic 12 amino acid peptide
- Pro-drug
- Constrictive activity via V-1 receptors
  - Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  - Increases effective blood volume
  - Reduces renin and angiotensin
    - Can lead to renal vasodilation
    - Can lead to improvement in serum creatinine
- V-2 agonist activity
  - Could possibly cause hyponatremia

Terlipressin + Albumin vs Midodrine/Octreotide + Albumin: Improvement in Renal Function

- Randomized controlled study (not blinded)
- 27 patients received terlipressin (IV 3 mg/24 hrs, progressively increased to 12 mg/24 hrs if no response)
- 22 patients received midodrine (orally at 7.5 mg TID with dose increased to max of 12.5 mg TID) and octreotide SC 100 mcg TID up to 200 mcg TID
- Both groups received albumin IV 1 g/kg of body weight on day 1 and 20-40 g/day thereafter

![Bar graph showing response to treatment](image)

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 up to 14 days unless one of the following occurred:
  - Verified HRS reversal (VHRSR) (decrease in SCr to \( \leq 1.5 \text{ mg/dL} \))
  - 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 \( \leq 1.5 \text{ mg/dL} \), at least 2 hours apart, with patient alive without RRT for \( \geq 10 \) days after the second SCr \( \leq 1.5 \text{ mg/dL} \)

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)

![Bar chart showing verified HRS reversal percentages for Terlipressin and Placebo groups.]

- **Terlipressin (N=199)**: 29.1%, **Placebo (N=101)**: 15.8%
- **P = 0.012**
- **Z score = 2.52618**. The final analysis is successful if the score is >1.97743.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)

Terlipressin (N=199) vs Placebo (N=101)

- Terlipressin: 31.7% (n=63), Placebo: 15.8% (n=16)

\[ P = 0.003^a \]

^aFrom 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).

^bPercentage of subjects with HRS reversal without RRT to day 30.

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Terlipressin (N=200)&lt;sup&gt;b&lt;/sup&gt; % (n)</th>
<th>Placebo (N=99)&lt;sup&gt;b&lt;/sup&gt; % (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.

<sup>a</sup>Up to 7 days posttreatment. <sup>b</sup>Subjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.

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)

- Terlipressin reduced need for RRT
- Terlipressin improved survival

<table>
<thead>
<tr>
<th></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 (Day 14)</td>
<td>10/60 (16.7%)</td>
<td>24/60 (40%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Real-World Use and Outcomes With Terlipressin

- Retrospective chart review of 225 patients diagnosed with HRS and treated with vasoconstrictors
- AKI defined by pre-treatment sCr
  - Mild: sCr <2.25 mg/dL
  - Moderate: 2.25 ≤sCr <3.5 mg/dL
  - Severe: sCr ≥ 3.5 mg/dL
- Primary outcome
  - Complete response (sCr ≤1.5 mg/dL)
  - Partial response (sCr reduction of ≥20% but sCr >1.5 mg/dL)
  - Overall response

Timeframe to Response

Disease status Event Total Median (95% CI)

- **Mild**: 53 67 7.0 (5.0-8.0)
- **Moderate**: 57 73 8.0 (6.0-8.0)
- **Severe**: 30 63 9.0 (7.0-11.0)

Days from start of treatment

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>64</td>
<td>55</td>
<td>42</td>
<td>31</td>
<td>27</td>
<td>22</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Moderate</td>
<td>73</td>
<td>73</td>
<td>73</td>
<td>71</td>
<td>67</td>
<td>60</td>
<td>49</td>
<td>37</td>
<td>28</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Severe</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>55</td>
<td>48</td>
<td>42</td>
<td>35</td>
<td>30</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
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Renal Response and Survival

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\(^3\)
- New AKI-HRS criteria enable earlier treatment at lower creatinine (1 mg/dL lower)\(^4\)
  - Baseline serum creatinine is a predictor of response to therapy

Prevention of AKI-HRS in Patients With Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Limiting lactulose dose to accomplish 2-3 BMs per day
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)

Take Home Points

- 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 earlier intervention
- Vasoactive agents (terlipressin and norepinephrine) can reverse HRS-AKI in a significant percentage of patients
- Terlipressin is superior to other agents in reversing HRS with expected survival benefits
  - Phase 3 CONFIRM US study results now available
THANK YOU!